HEALTH EVIDENCE REVIEW COMMISSION (HERC)

COVERAGE GUIDANCE: UPPER ENDOSCOPY FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) AND DYSPEPSIA SYMPTOMS

As posted for public comment 6/27/2013

HERC COVERAGE GUIDANCE

Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is not recommended for coverage in patients less than 50 years of age unless the patient has persistent symptoms following completion of an appropriate course of PPI therapy or an H. pylori test and treat protocol (strong recommendation).

Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is recommended for coverage in patients at least 50 years of age (strong recommendation).

Repeat endoscopy within nine years is not recommended for coverage for patients with dyspepsia after non-malignant findings on initial endoscopy (weak recommendation).

This guidance does not apply to coverage of endoscopy for patients presenting with "alarm symptoms" including, but not limited to, anemia, weight loss, and dysphagia.

Note: Definitions for strength of recommendation are provided in Appendix A GRADE Element Description

RATIONALE FOR GUIDANCE DEVELOPMENT

The HERC selects topics for guideline development or technology assessment based on the following principles:

- Represents a significant burden of disease
- Represents important uncertainty with regard to efficacy or harms
- Represents important variation or controversy in clinical care
- Represents high costs, significant economic impact
- Topic is of high public interest

Coverage guidance development follows to translate the evidence review to a policy decision. Coverage guidance may be based on an evidence-based guideline developed by the Evidence-based Guideline Subcommittee or a health technology assessment developed by the Heath Technology Assessment Subcommittee. In addition, coverage guidance may utilize an existing evidence report produced by one of HERC's trusted sources, generally within the last three years.

EVIDENCE SOURCE

DRAFT

Liu, R., Kriz, H., Thielke, A., Vandegriff, S., & King, V. (2012). *Upper endoscopy for gastroesophageal reflux disease (GERD) and upper gastrointestinal (GI) symptoms*. Olympia: Washington State Health Authority Health Technology Assessment Program. Retrieved February 21, 2013, from http://www.hta.hca.wa.gov/gerd.html

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

SUMMARY OF EVIDENCE

Clinical Background

Gastroesophageal reflux disease (GERD) is the most common outpatient gastrointestinal diagnosis in the United States, with a prevalence of 10% to 58.3% and an annual incidence of 0.38% to 0.45%. The Montreal consensus panel, an international Consensus Group tasked with developing a global definition and classification of GERD, reached strong consensus in defining GERD as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications”. Common symptoms of GERD include heartburn (defined as a burning sensation behind the breastbone), regurgitation and chest pain. Obesity; the presence of a hiatal hernia; and the use of estrogen, nitrates, anticholinergics, and tobacco products are considered risk factors for GERD. Gastroesophageal reflux disease can lead to a decreased quality of life and to more severe conditions such as esophagitis, Barrett’s esophagus, and adenocarcinoma of the esophagus.

Dyspepsia is estimated to range in prevalence in the United States from 2.9 to 34.4%. The Rome III Committee defines dyspepsia as having one or more of the following symptoms: epigastric pain or burning; postprandial fullness; and/or early satiety. Other dyspeptic symptoms may include nausea and vomiting, upper abdominal bloating, heart burn, and regurgitation. Dyspepsia symptoms are distinguished from GERD as not being “troublesome” enough, referring to the Montreal definition of GERD; however, many authors have used the terms interchangeably.

The signs and symptoms of GERD, dyspepsia, and other more severe conditions such as Barrett’s esophagus, can be very similar, and diagnostic procedures can be used to establish a diagnosis and rule out other possible conditions. Diagnostic procedures for dyspepsia and GERD can include questionnaires, empiric therapeutic trial, pH monitoring, upper endoscopy, and/or double contrast barium swallow. Empiric therapeutic trial is a commonly employed strategy for patients presenting with GERD. This includes both an empiric trial of proton pump inhibitors (PPI) and test-and-treat for *Helicobacter pylori (H. pylori)* An empiric trial of PPIs typically includes twice daily dosing for four weeks, and a daily dose of 40 to 80mg of omeprazole is the most

common PPI regimen used in clinical empiric therapy studies. The sensitivity and specificity of this PPI test ranges from 62 to 92% and 36 to 100%, respectively.

Evidence Review

Effectiveness of Early Treatment Strategies

With regard to the effectiveness of early treatment strategies for GERD that include upper endoscopy compared with empiric medical management, one good quality systematic review including two separate meta-analyses was identified. One evaluated early endoscopy versus empiric PPI and the other evaluated early endoscopy versus test-and-treat for *H. pylori.* The first meta-analysis included five RCTs and found no difference in symptomatic cure at 12 months between endoscopy and PPI arms. The second meta-analysis, also including five RCTs, was first done by pooling trial-level data. This analysis found no difference in effect (RR 0.95, 95% CI 0.79 to 1.15), but a high degree of statistical heterogeneity. When an alternate analysis of these same five studies was done using individual patient data, there was no longer statistical heterogeneity and a small but statistically significant benefit to upper endoscopy emerged (OR 0.75, 95% CI 0.58 to 0.96; RR 0.95, 95% CI 0.92 to 0.99).

A single fair quality prospective cohort study of 70 patients found that 24-hour pH monitoring is the most accurate single diagnostic test for GERD, when a concordance of three separate tests (omeprazole challenge, endoscopy, histology, pH monitoring) is taken as the gold standard. However, the authors note that there are barriers to its widespread use including invasiveness, cost, and availability. A serial application of an omeprazole challenge test, endoscopy, and finally histopathology achieves a sensitivity of 100% for GERD diagnosis.

Overall, considering all the available evidence from the systematic review plus the cohort study, there does not appear to be a clinically relevant benefit of prompt upper endoscopy over test and treat strategies or empiric PPI therapy for uninvestigated GERD symptoms in the primary care setting. (*Overall strength of evidence: High)*

Indications for Early Endoscopy

When considering whether there are clinical signs and symptoms that may be useful to identify patients for whom early endoscopy improves health outcomes, one good quality systematic review of 57,363 patients in 17 prospective cohort studies was identified. They found that alarm symptoms[1], clinical opinion, and computer modeling programs based on symptom questionnaires were all unreliable predictors of gastrointestinal

[1] Weight loss, dysphagia, anemia

malignancy. Sensitivity ranged from 0% to 83% while specificity varied from 40% to 98%.

A good quality prospective cohort study found cancer in 0.9% of patients presenting with uncomplicated dyspepsia (i.e., without alarm symptoms) and the findings suggest that risk is correlated with age greater than 35 for males and greater than 57 for females. A fair quality prospective cohort study determined that American Society of Gastroenterologists (ASGE) guideline criteria (indications for endoscopy) were poorly correlated with clinically relevant endoscopic findings, although having a guideline indication does marginally increase the pre-test probability of endoscopy (from 45% to 47%), while not having one lowers it (from 45% to 29%). A second fair-quality prospective cohort study in the setting of open-access endoscopy found that 15% of the patients with esophagogastric carcinoma did not present with alarm symptoms and may have suffered delayed diagnosis without early endoscopy; however, there was an unusually high prevalence (3%) of cancer in the study population. Finally, a fair-quality prospective cohort study of primary care patients with uninvestigated dyspepsia found that Barrett's esophagus was most likely in patients who were male, greater than 50 years old, had symptoms of at least 5 to 10 years duration, and suffered predominantly from reflux.

The authors of the systematic review noted above suggest that, in the absence of compelling predictors, the concept of "alarm symptoms" should not be abandoned at this time. They suggest age greater than 55 as "the most logical alternative strategy… because the incidence of upper GI malignancy is negligible in Western populations at younger ages and only rises in prevalence above the age of 55 years." In contrast, the authors of the good quality cohort study suggest that age should be lower (35) for males and could be higher (57) for females. (*Overall strength of evidence: Moderate)*

<u>Repeat Endoscopy</u>

With regard to whether there are diagnoses for which repeat endoscopy is indicated, only one study, a prospective cohort study of good quality, addressed the question. This study evaluated the utility of repeat endoscopy in patients who initially presented with dyspeptic symptoms and had non-malignant endoscopic findings. About a third of these patients underwent a subsequent endoscopy within nine years of the index study. The results of these later endoscopies are not known; however, patients who had further endoscopy were neither more nor less likely than other patients to be symptomatic eight to nine years after the index study (χ^2=0.6, df=1, $p > 0.05$). Overall, evidence is insufficient to suggest repeat endoscopy to any patients with initial dyspepsia who have non-malignant findings on their index endoscopy. (*Overall strength of evidence: Low)*

<u>Harms of Endoscopy</u>

None of the included studies addressed harms. According to the authors of one economic evaluation, most harms of endoscopy are cardiorespiratory in nature; that is, related to the procedure sedation rather than the endoscope itself. These authors used a 0.02% incidence of severe harms and modeled their economic assumptions on the surgical repair of perforation. No data was identified on harms associated with empiric acid-suppression or *H. pylori* test-and-treat. (*Overall strength of evidence: Insufficient)*

Subpopulations

Age was the only factor associated with differential effectiveness in one good quality meta-analysis. The authors of this study performed subgroup analyses based on age, gender, predominant symptom, and presence of *H. pylori*. There was a small but statistically significant benefit of endoscopy in patients 50 years of age and older (RR=0.90, 95% CI 0.82 to 1.00, $p < 0.05$); no other associations were found. A good-quality prospective cohort study found that patients with malignancy were on average 20 years older than patients without malignancy ($p < 0.001$). A fair-quality prospective cohort study also found increasing prevalence of malignancy with rising age. In a good quality economic evaluation simulation model, relative effectiveness of interventions was similar, but resulted in slightly fewer additional quality adjusted life years (QALY) in hypothetical 30 year olds than in hypothetical 60 year olds. A poor quality retrospective chart review of VA patients failed to find any correlation between significant endoscopic findings (Barrett's esophagus and/or erosive esophagitis) and age, gender, race, or NSAID use. (*Overall strength of evidence: Moderate [Age], Insufficient [All others])*

Cost-effectiveness of Endoscopy Compared to Other Treatment Strategies

With the exception of empiric therapy for US 30 year olds, all five good quality studies, one of two fair quality studies, and one of three poor quality studies favored *H. pylori* test-and-treat as the most cost-effective strategy for adults with uninvestigated symptoms of dyspepsia and/or GERD. Only two studies, both of good quality, evaluated the cost-effectiveness of different management strategies for new upper gastrointestinal symptoms in a US population. In a simulation model, empiric PPI was the strategy of choice for 30 year old patients, and test-and-treat for *H. pylori* was the most cost-effective intervention for 60 year olds. A decision analysis looked only at patients less than 45 years of age, and determined that adding a 6-week trial of PPI to the test-and-treat strategy improved its cost-effectiveness. A good quality economic evaluation of Canadian individual patient data concluded that no one strategy was the most clearly cost-effective, but at a clinically relevant willingness-to-pay threshold of CAN$30,000 to 70,000 per QALY, omeprazole treatment based on the CanDys protocol (which incorporates test-and-treat for those without heartburn or reflux as the predominant symptom) was the most cost-effective. Two other good quality models also favored the test-and-treat approach, along with one fair and one poor quality RCT. One fair quality decision analysis favored a screening questionnaire followed by prompt endoscopy for

DRAFT

high-risk patients. Two poor quality RCTs found empiric PPI to be the most cost-effective alternative, but did not include comparison to *H. pylori* testing and treatment. There were no economic studies that found prompt endoscopy to be the most cost-effective intervention. (*Overall strength of evidence: Moderate)*

[Evidence Source]

Evidence Summary

Overall, the evidence does not point to a clinically relevant benefit of prompt upper endoscopy over test-and-treat strategies or empiric PPI therapy for uninvestigated GERD symptoms in the primary care setting. Alarm symptoms, clinical opinion, and computer modeling programs based on symptom questionnaires are all unreliable predictors of gastrointestinal malignancy. The harms of endoscopy, or of any of the treatment strategies for GERD or dyspepsia, have not been well documented in this literature base. There is an increasing prevalence of malignancy with rising age, and there may be a small benefit of endoscopy over other initial treatment strategies in patients over 50 based on one trial. Test-and-treat for *H. pylori* is likely the most cost-effective strategy for adults with uninvestigated symptoms of dyspepsia and/or GERD.

DRAFT

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	Balance between desirable and undesirable effects	Quality of evidence*	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
Endoscopy as initial evaluation for new onset GERD or dyspepsia in patients under 50 or 55	No net benefit compared to other treatment strategies	High	Other treatment strategies are less costly	Low variability. Most would want to avoid endoscopy; some would prefer definite diagnosis before treatment	*Dr. Schembre agrees with the coverage recommendation, but has concerns regarding high risk individuals on long-term PPI therapy without endoscopy*	Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is not recommended for coverage in patients less than 50 years of age unless the patient has completed an appropriate course of PPI therapy or an H. pylori test and treat protocol (strong recommendation).
Endoscopy as initial evaluation for new onset GERD or dyspepsia in patients over 50 or 55	Small net benefit compared to other treatment strategies	Moderate	Endoscopy moderately more costly	Moderate variability	*Concurs with this recommendation*	Upper endoscopy for uninvestigated dyspepsia or GERD symptoms is recommended for coverage in patients at least 50 years of age (strong recommendation)

DRAFT

Indication	Balance between desirable and undesirable effects	Quality of evidence*	Resource Allocation	Values and preferences	Expert Input	Coverage Recommendation
Repeat endoscopy after initial endoscopy for GERD with non-malignant findings	No apparent benefit, small harms	Insufficient	Endoscopy moderately more costly	Moderate variability	*Does not support this recommendation. At the least, would recommend 5 years as a more reasonable restriction.*	Repeat endoscopy within nine years is not recommended for coverage for patients with dyspepsia after non-malignant findings on initial endoscopy (weak recommendation).

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

Note: GRADE framework elements are described in Appendix A

DRAFT

POLICY LANDSCAPE

Eight quality measures were identified when searching the National Quality Measures Clearinghouse. Five are sponsored by the American Gastrenterological Association Institute, while three are sponsored by the Australian Council on Healthcare Standards. None have been endorsed by the National Quality Forum. The five American measures are listed below:

1. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 and older with the diagnosis of GERD who have been prescribed chronic proton pump inhibitor (PPI) or histamine H_2 receptor antagonist (H_2 RA) therapy who received an assessment of their GERD symptoms within 12 months

2. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 seen for an initial evaluation of GERD who did not have a barium swallow test ordered

3. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 and older with the diagnosis of GERD, seen for an initial evaluation, who were assessed for the presence or absence of the following alarm symptoms: involuntary weight loss, dysphagia, and GI bleeding

4. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 and older with the diagnosis of GERD or heartburn whose endoscopy report indicates a suspicion of Barrett's esophagus who had a forceps biopsy performed

5. Gastroesophageal reflux disease (GERD): percentage of patients aged 18 and older seen for an initial evaluation with at least one alarm symptom who were either referred for upper endoscopy or had an upper endoscopy performed

COMMITTEE DELIBERATIONS – HTAS

COMMITTEE DELIBERATIONS – VBBS

DRAFT

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.

DRAFT

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 of evidence across studies for the treatment/outcome

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain.

DRAFT

Appendix B. Applicable Codes

CODES	DESCRIPTION
ICD-9 Diagnosis Codes	
530.1	Esophagitis
530.11	Reflux esophagitis
530.12	Acute esophagitis
530.19	Other esophagitis
530.2	Ulcer of esophagus
530.21	… with bleeding
530.3	Stricture and stenosis of esophagus
530.81	Esophageal reflux
530.85	Barrett's esophagus
530.89	Other specified disorders of esophagus
530.9	Unspecified disorder of esophagus
535	Gastritis and duodenitis
535.0	Acute gastritis
535.2	Gastric mucosal hypertrophy
535.3	Alcoholic gastritis
535.4	Other specified gastritis
535.5	Unspecified gastritis and gastroduodenitis
536.2	Persistent vomiting
536.8	Dyspepsia and other specified disorders of function of stomach
536.9	Unspecified functional disorder of stomach
786.5	Chest pain
786.59	Other chest pain
787.1	Heartburn
787.2	Dysphagia
787.21	…oral phase
787.22	… oropharyngeal phase
787.23	… pharyngeal phase
787.24	… pharyngoesophageal phase
787.29	Other dysphagia
789	Other symptoms involving abdomen and pelvis
789.06	… epigastric
789.07	… generalized
789.09	… other specified site
ICD-9 Volume 3 (Procedure Codes)	
42.23	Other esophagoscopy
42.24	Closed [endoscopic] biopsy of esophagus
44.13	Other gastroscopy
44.14	Closed [endoscopic] biopsy of stomach

DRAFT

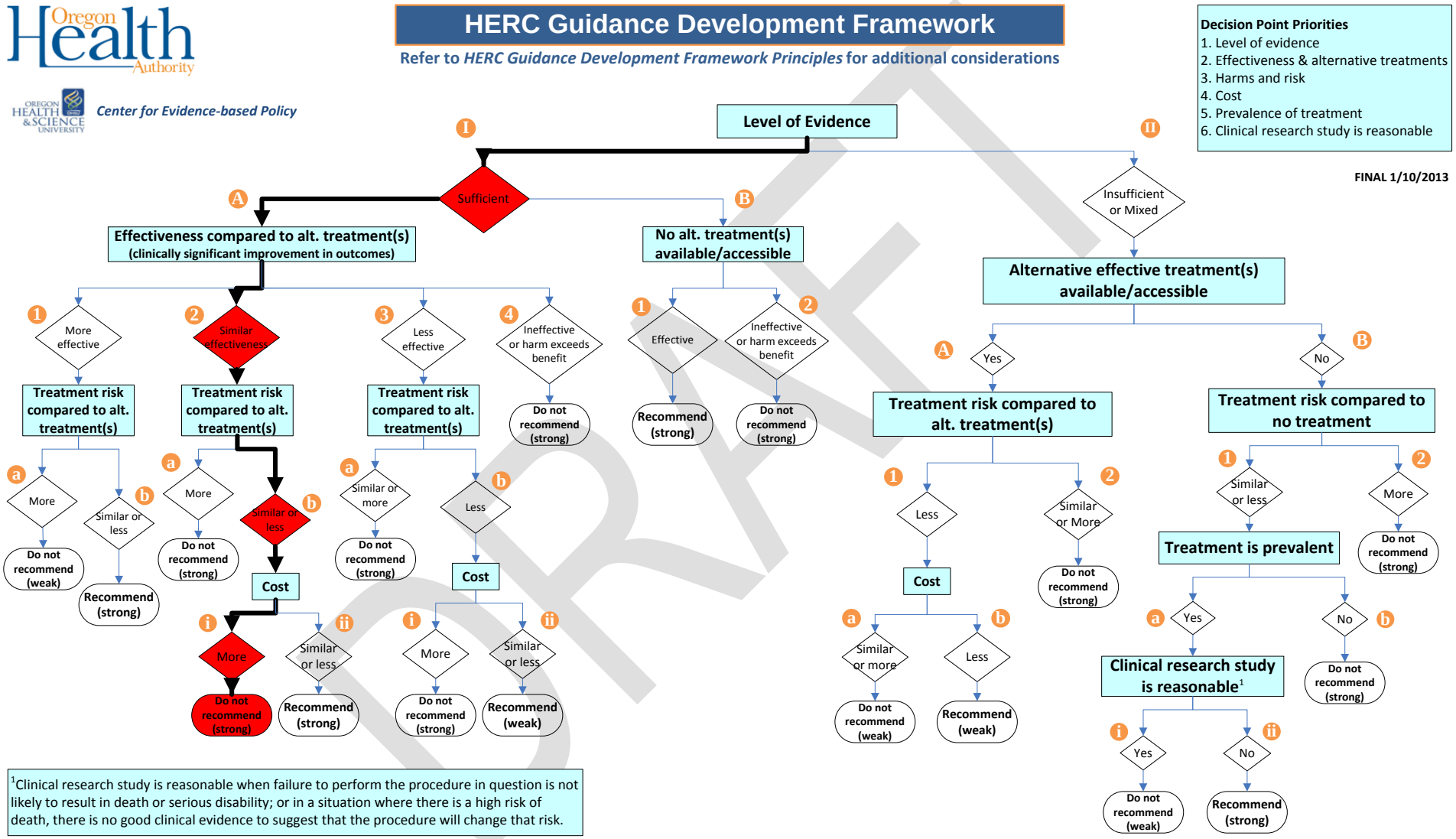
CODES	DESCRIPTION
45.13	Other endoscopy of small intestine
45.14	Closed [endoscopic] biopsy of small intestine
45.16	Esophagogastroduodenoscopy [EGD] with closed biopsy
CPT Codes	
43200	Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)
43202	…with biopsy, single or multiple
43235	Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)
43239	…with biopsy, single or multiple
HCPCS Level II Codes	
None	

Note: Inclusion on this list does not guarantee coverage

DRAFT

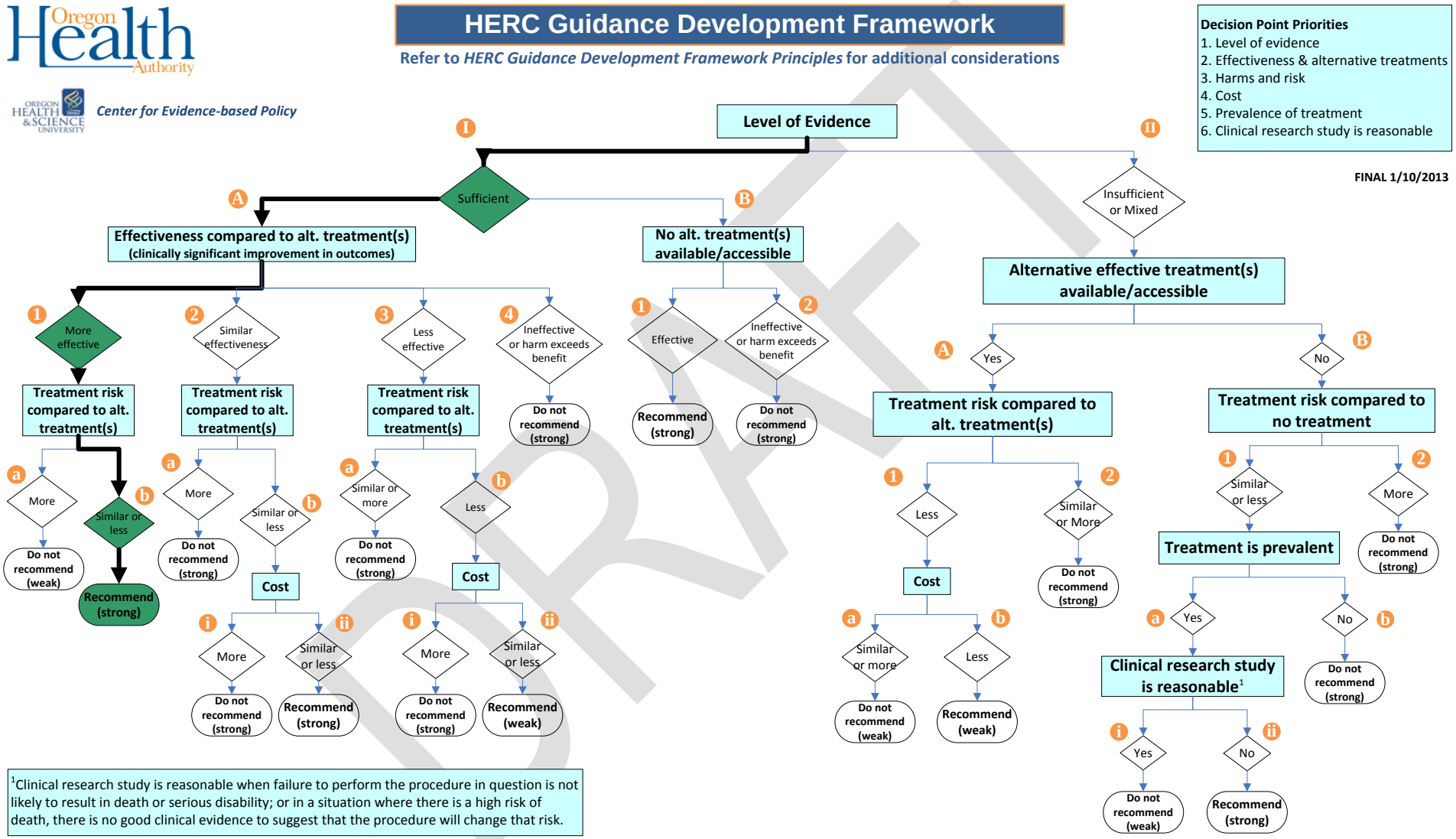
Appendix C. HERC Guidance Development Framework

Endoscopy for Evaluation of Dyspepsia/GERD under Age 50/55 (Prior to PPI or Test and Treat)



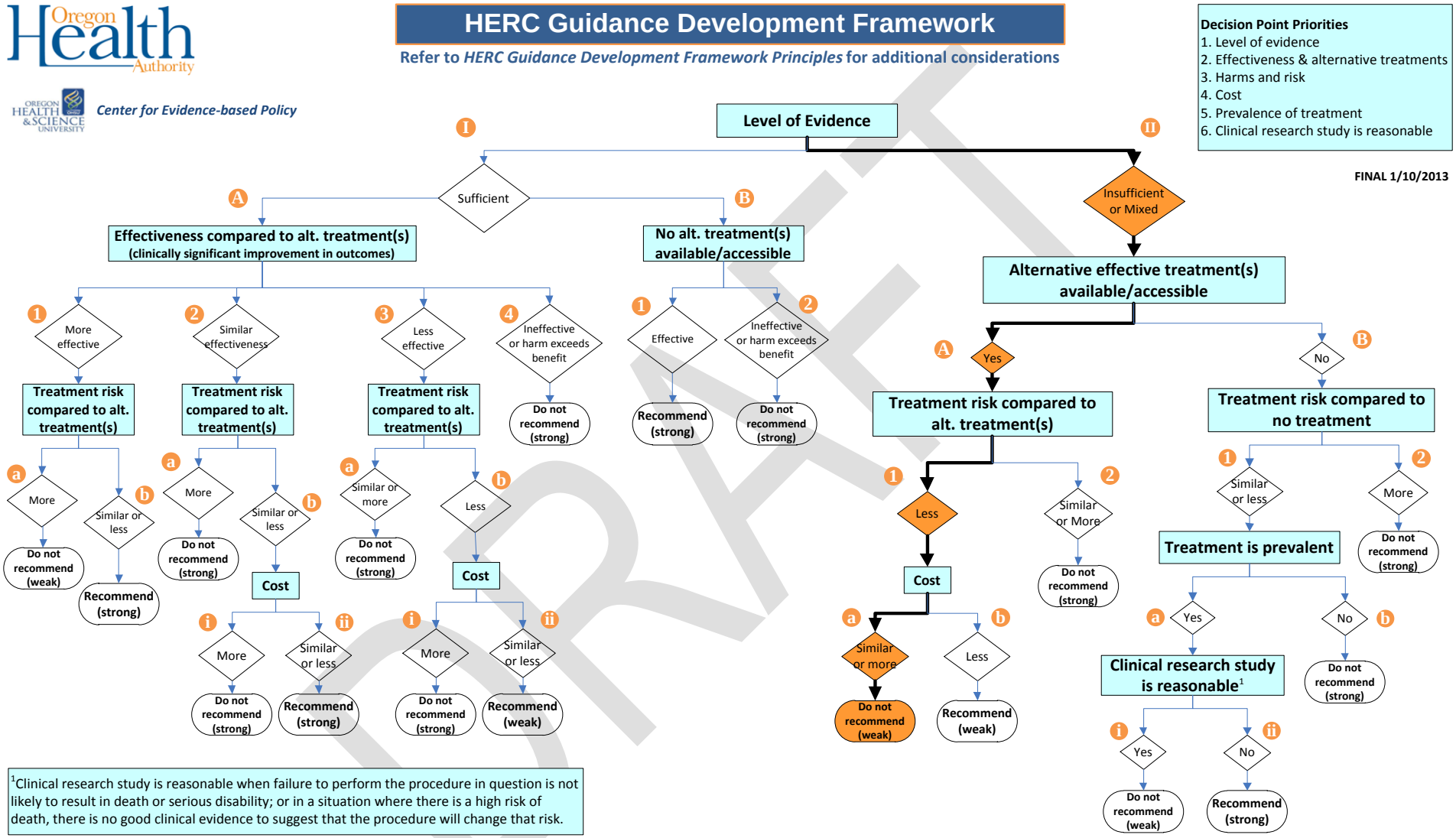
DRAFT

Endoscopy for Evaluation of Dyspepsia/GERD after age 50/55 (Compared to PPI or Test and Treat)



DRAFT

Repeat endoscopy within 9 years after initial endoscopy for GERD with non-malignant findings



DRAFT