# HEALTH EVIDENCE REVIEW COMMISSION (HERC)

## COVERAGE GUIDANCE: BIOMARKER TESTS OF CANCER TISSUE FOR PROGNOSIS AND POTENTIAL RESPONSE TO TREATMENT

**As posted for public comment 2/25/2015 to 8 a.m. 3/30/2015**

### HERC Coverage Guidance

Oncotype DX is recommended for coverage in early stage breast cancer when used to guide adjuvant chemotherapy treatment decisions for women who are lymph node negative (strong recommendation),

The following genetic tests of cancer tissue are recommended for coverage (strong recommendation):

- BRAF gene mutation testing for melanoma
- Epidermal growth factor receptor (EGFR) gene mutation testing for non-small-cell lung cancer
- KRAS gene mutation testing for colorectal cancer

The following genetic tests of cancer tissue are not recommended for coverage (weak recommendation):

- Mammaprint, ImmunoHistoChemistry 4 (IHC4), and Mammostrat for breast cancer
- Prolaris and Oncotype DX for prostate cancer
- BRAF, microsatellite instability (MSI), and Oncotype DX for colorectal cancer
- KRAS for lung cancer
- Urovysion for bladder cancer
- Oncotype DX for lymph node-positive breast cancer

The use of multiple molecular testing to select targeted cancer therapy is not recommended for coverage (weak recommendation).

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

## RATIONALE FOR GUIDANCE DEVELOPMENT

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

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

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

# EVIDENCE SOURCES

## Trusted sources


Blue Cross Blue Shield (BCBS). (2014). *Gene Expression Analysis for Prostate Cancer Management.* Chicago, IL: BCBS. Retrieved on October 21, 2014, from http://www.bcbs.com/blueresources/tec/vols/28/28_11.pdf

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Bunker, K., Kriz, H., Liu, R., Thielke, A., Lorish, K., & King, V. (2011). Oncotype DX Assay for Breast Cancer. Portland, OR: Center for Evidence-based Policy, Oregon Health and Science University.

Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). *Oncotype DX in women and men with ER-positive, HER2-negative early stage breast cancer who are lymph node-positive: a review of clinical effectiveness and guidelines*. Ottawa, CA: CADTH. Retrieved on October 21, 2014, from http://www.cadth.ca/media/pdf/htis/mar-2014/RC0517_OncotypeDX_NodePos%20Final.pdf

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McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R et al (2014). *Safety and efficacy of vemurafenib in BRAFV600$^{E}$ and BRAFV600$^{K}$ mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study*. The Lancet Oncology, 15(3), 323-332. Retrieved on February 10, 2015, from http://dx.doi.org/10.1016/S1470-2045(14)70012-9.

(http://www.sciencedirect.com/science/article/pii/S1470204514700129)Meleth, S., Reeder-Hayes, K., Ashok, M., Clark, R., Funkhouser, W., Wines, R., et al. (2014). *Technology assessment of molecular pathology testing for the estimation of prognosis for common cancers*. Rockville, MD: Agency for Healthcare Research and Quality. Retrieved on October 21, 2014, from http://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id94TA.pdf

Mujoomdar M, Moulton K, & Spry C. (2010). *Epidermal Growth Factor Receptor Mutation Analysis in Advanced Non-Small Cell Lung Cancer: A Review of the Clinical Effectiveness and Guidelines*. Ottawa: CADTH. Retrieved on December 10, 2014, from http://www.cadth.ca/media/pdf/M0017_EGFR_Testing_for_NSCLC_e.pdf

National Institute for Health and Care (NICE). (2014). *Early and locally advanced breast cancer*. London, UK: NICE. Retrieved on November 5, 2014, from http://www.nice.org.uk/guidance/cg80/resources/guidance-early-and-locally-advanced-breast-cancer-pdf

National Institute for Health and Care Excellence (NICE). (2013). *EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer.* NICE diagnostics guidance 9. London, UK: NICE. Retrieved on December 9, 2014, from http://www.nice.org.uk/guidance/dg9/resources/guidance-egfrtk-mutation-testing-in-adults-with-locally-advanced-or-metastatic-nonsmallcell-lung-cancer-pdf

National Institute for Health and Care (NICE). (2013). *Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat*. London, UK: NICE. Retrieved on October 21, 2014, from http://www.nice.org.uk/guidance/dg10/resources/guidance-gene-expression-profiling-and-expanded-immunohistochemistry-tests-for-guiding-adjuvant-chemotherapy-decisions-in-early-breast-cancer-management-mammaprint-oncotype-dx-ihc4-and-mammostrat-pdf

Terasawa T, Dahabreh I, Castaldi PJ, Trikalinos TA. (2010). *Systematic reviews on selected pharmacogenetic tests for cancer treatment: CYP2D6 for tamoxifen in breast cancer, KRAS for anti-EGFR antibodies in colorectal cancer, and BCR-ABL1 for tyrosine kinase inhibitors in chronic myeloid leukemia. Technology Assessment Report.* (Prepared by Tufts Evidence-based Practice Center under contract number HHSA 290 2007 100551). Rockville, MD: Agency for Healthcare Research and Quality. Retrieved on December 10, 2014, from http://www.cms.gov/medicare-coverage-database/details/technology-assessments-details.aspx?TAId=76&bc=BAAgAAAAAAAA&

## Additional sources

Febbo, P; Ladanyi, R; Aldape, K; De Marzo, A; Hammond, E; Hayes, D, et al. (2011). *NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology.* Journal of National Comprehensive Cancer Network Vol 9, Suppl 5:S1–S32.

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

# EVIDENCE OVERVIEW: BREAST CANCER

## Clinical background

Breast cancer is the second most common cancer among women and one of the leading causes of death in the United States. The most recent estimates from the Centers for Disease Control and Prevention report that in 2007, 202,964 women in the United States were diagnosed with breast cancer, and 40,598 women died from breast cancer. However, earlier detection, better risk prediction models, and advancements in preventive therapies are leading to improved outcomes for women diagnosed with breast cancer.

The spread of cancer is described in terms of breast cancer staging. Staging is determined by the size of the tumor and the presence and size of metastases. Stages are defined as 0, I (A or B), II (A or B), III (A, B, or C), or IV. Early stage breast cancer (stage I or stage II) has not spread to distant lymph nodes, but cancer cells may be found in nearby lymph nodes. These lymph nodes include ones in the axilla or near the breast bone.

Treatment for women with early stage breast cancer includes primary therapy (e.g., lumpectomy, mastectomy), but also may include adjuvant hormone therapy and chemotherapy. Studies from the National Surgical Adjuvant Breast and Bowel Project indicate that the probability of distant recurrence is 15% at 10 years in women treated only with tamoxifen. Since more than 15% of women with early stage breast cancer are receiving chemotherapy, this indicates that many women who receive adjuvant chemotherapy would be disease-free without this added therapy. This suggests that there is a population of low-risk patients that derives little additional therapeutic benefit from chemotherapy, and may be at risk of harm from this treatment.

Among women with early stage breast cancer who have undergone any adjuvant therapy, the recurrence rate has been found to be 11% at five years and 20% at 10 years post-treatment. Stratified by the stage of the cancer at diagnosis, the five year residual risk of recurrence is reported to be 7% among those diagnosed with stage I cancer (95% CI: 3 to 15%), 11% among those diagnosed with stage II cancer (95% CI: 9 to 13%), and 13% among those diagnosed with stage III cancer (95% CI: 10 to 17%).

There are a variety of clinical decision-making tools currently in use to estimate breast cancer recurrence risk, including the St. Gallen consensus recommendations, the National Comprehensive Cancer Network guidelines (NCCN), Adjuvant! Online, and the Nottingham Prognostic Index (NPI). These protocols incorporate various factors such as patient demographics (e.g., age, menopausal status, comorbidity) and tumor data (e.g., staging, size, estrogen-receptor (ER) status, number of positive lymph nodes, human epidermal growth factor-2 receptor (HER2) status) to estimate risk and guide choice of treatments.

Although each tool has separately been shown to have predictive ability and is supported by clinical trial data, in comparative studies these tools often disagree about a particular patient's risk, and none of them is considered the gold standard of prediction. Treatment decisions, particularly whether or not to pursue adjuvant chemotherapy, are made partially based on these risk estimates. With advances ine cancer therapy, it is increasingly important to be able to predict which patients will benefit from particular types of treatment. Multiple genomic tests have been developed for this purpose, of which four will be reviewed here.

## Technology description

### NICE (2013): Gene Expression Profiling and Immunohistochemistry Tests for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer: MammaPrint®, Oncotype DX®, IHC4, Mammostrat®

Some gene expression profiling tests work by identifying and quantifying mRNA transcripts in a specific tissue sample. Because only a fraction of the genes encoded in the genome of a cell are transcribed into mRNA, gene expression profiling provides information about the activity of genes that give rise to these mRNA transcripts. Other gene expression profiling tests work by measuring levels of cDNA, which is synthesized from mRNA. There are a range of different techniques for measuring mRNA levels in breast cancer tumor samples, including real-time reverse transcription polymerase chain reaction (RT-PCR) and DNA microarrays.

Different tests use different protocols for preparing the samples (for example, formalin fixation, paraffin embedding, snap freezing and fresh samples) and different methods for preparing the RNA. Furthermore, there are different algorithms for combining the raw data into a summary profile. All of these factors can affect the reproducibility and reliability of gene expression profiling tests.

- MammaPrint is based on microarray technology and uses an expression profile of 70 genes. MammaPrint is intended as a prognostic test for women of all ages, with LN− and LN+ (up to 3 nodes positive) breast cancer with a tumor size of 5 cm or less. MammaPrint is used to estimate the risk of distant recurrence of early breast cancer. It stratifies patients into 2 distinct groups – low risk (good prognosis) or high risk (poor prognosis) of distant recurrence. MammaPrint has been cleared by the Food and Drug Administration as an In Vitro Diagnostic Multivariate Index Assay. The test uses fresh or formalin-fixed paraffin-embedded samples that are processed centrally at laboratories run by the manufacturer in the USA or The Netherlands.

- Oncotype DX® quantifies the expression of 21 genes in breast cancer tissue by RT-PCR. It predicts the likelihood of recurrence in women of all ages with newly diagnosed stage I or II, ER+, LN− or LN+ (up to 3 nodes positive) breast cancer treated with tamoxifen. The test assigns the breast cancer a continuous recurrence score (RS) and a risk category – low (RS<18), intermediate (18≤RS≤30) or high (RS≥31). The test also reports ER, progesterone receptor (PR) and HER2 status. The test uses formalin-fixed paraffin-embedded samples that are processed centrally at a laboratory run by the manufacturer in the USA.

Immunohistochemistry tests measure protein levels in the tumor sample rather than RNA or cDNA. Some of these tests offer the advantage of using existing immunohistochemical markers (such as ER and HER2), which are routinely tested in UK pathology departments. The term 'expanded' has been used to describe the immunohistochemistry tests evaluated in this assessment that are used in addition to standard immunohistochemistry testing (such as ER and HER2) for early invasive breast cancer. Immunohistochemistry uses staining to identify protein expression and reports the level of protein expression in tumor tissue. Differences in immunohistochemistry values can be caused by variability in several factors, including fixation of tissue, antigen retrieval (used to enhance staining), reagents, and interpretation.

- IHC4 measures the levels of 4 key proteins (ER, PR, HER2 and Ki-67) in addition to classical clinical and pathological variables (for example, age, nodal status, tumour size and grade) and calculates a risk score for distant recurrence using an algorithm. Quantitative assessments of ER, PR, and Ki-67 are needed for the IHC4 test. An online calculator for IHC4 is in development. The test uses formalin-fixed paraffin-embedded samples that can be processed in local NHS laboratories.

- Mammostrat uses 5 immunohistochemical markers (SLC7A5, HTF9C, P53, NDRG1 and CEACAM5) to stratify patients into risk groups to inform treatment decisions. These markers are independent of one another and do not directly measure either proliferation or hormone receptor status. The test calculates the relative risk of recurrence by using a weighted algorithm that is interpreted in the context of published clinical studies of appropriate patient populations. Patients are classified into 3 risk categories: prognostic index ≤0 defined as the 'low risk' group; prognostic index >0 and ≤0.7 defined as the 'moderate-risk' egroup; prognostic index >0.7 defined as the 'high risk' group. The test uses formalin-fixed paraffin-embedded samples that are processed centrally at a laboratory run by the manufacturer in the USA.

## Evidence review

### NICE (2014): Early and Locally Advanced Breast Cancer

The NICE Cancer Service Guidance, *Improving outcomes in breast cancer*, recommends that women at intermediate or high risk of recurrence who have not had neoadjuvant chemotherapy should normally be offered multi-agent chemotherapy, which includes anthracyclines. The *Early and locally advanced breast cancer: diagnosis and treatment* guideline recommends that adjuvant therapy should be considered for all patients with early invasive breast cancer after surgery, based on assessment of the prognostic and predictive factors, and the potential benefits and side effects of the treatment. These guidelines do not refer to the use of gene expression profiling and expanded immunohistochemistry tests to aid decision making, but recommend that decisions should be made following discussion of these predictive and prognostic factors with the patient and that Adjuvant! Online should be considered to support estimations of indiviedual prognosis and the absolute benefit of adjuvant treatment. The NPI is

also commonly used locally to aid decisions about chemotherapy for patients with early stage breast cancer.

The following outcomes were evaluated for the four included tests:

- Analytical validity (the ability of the test to accurately and reliably measure the expression of mRNA or proteins by breast cancer tumor cells
- Clinical valiedity (prognostic ability, or the degree to which the test can accurately predict the risk of an outcome, such as the risk of distant metastases in 10 years)
- Clinical utility, defined as the ability of the test to improve clinical outcomes such as overall survival. This includes direct harms arising from the test, reclassification of risk compared with existing tools, its impact on clinical decision-making and the ability of the test to predict benefit from chemotherapy.

### *MammaPrint®*

Systematic reviews indicated that evidence relating to the clinical validity of MammaPrint® was not always conclusive nor supported the prognostic value of the test. Seven additional studies of MammaPrint® were identified by the guidance authors. Of these, four on the clinical validity of MammaPrint® demonstrated that the MammaPrint® score is a strong independent prognostic factor, and may provide additional value to standard clinic-pathological measures. There were no prospective studies of the impact of MammaPrint® on long-term outcomes such as overall survival. Six studies with data on the clinical utility of MammaPrint® were identified, and reported a high level of discordance between MammaPrint® and current classification, although these studies did not demonstrate how this would impact on treatment decisions.

In summary, robust evidence of clinical utility is not available for MammaPrint® so it is not yet clear whether using the test will improve the use of adjuvant chemotherapy in the management of breast cancer in the UK. Most studies of MammaPrint® were retrospective in design, used small sample sizes and had heterogeneous patient populations; some studies included only premenopausal women. The evidence for MammaPrint® is based on the use of the test with fresh samples. It is not clear whether this evidence would apply if the test were used on formalin-fixed paraffin-embedded samples.

### *Oncotype DX®*

Systematic reviews reported evidence that the Oncotype DX® recurrence score was significantly correlated with disease-free survival and overall survival. Furthermore, the recurrence score was shown to be a better predictor of distant recurrence at 10 years than traditional clinico-pathological predictors. The evidence on clinical utility was limited. One study demonstrated a significantly increased benefit from the use of chemotherapy in the Oncotype DX® high-risk group compared with the low-risk group.

The guidance authors identified 12 additional studies of Oncotype DX® supporting the prognostic ability of Oncotype DX®. One large-scale UK study in post-menopausal women with ER+, LN− early bereast cancer found that an increase in risk score was significantly associated with an increased risk of distant recurrence. Furthermore, the evidence base has been extended

to include the LN+ population. No prospective studies of the impact of Oncotype DX® on long-term outcomes such as overall survival were identified. Four studies presented further evidence on the impact of Oncotype DX® on clinical decision making. These indicated that the use of Oncotype DX leads to changes in treatment decisions for between 32% and 38% of patients.

Four publications reported evidence that Oncotype DX® predicts benefit from chemotherapy. The first evidence of improvements in quality of life and reduced patient anxiety as a result of using Oncotype DX® have been reported, although the studies had small sample sizes.

In summary, Oncotype DX® is considered to have the most robust evidence base of the tests reviewed in this guidance, with data on the analytical validity, clinical validity, and clinical utility of the test. The studies varied considerably in their size, design and patient populations. Many of the Oncotype DX studies were small and retrospective.

### *IHC4*

No studies of analytical validity of IHC4 were identified. One study on clinical validity was identified, which reported that the IHC4 score is a highly significant predictor of distant recurrence. No prospective studies of the impact of IHC4 on long-term outcomes such as overall survival, or its ability to change treatment decisions or predict chemotherapy benefit weere identified. In summary, the guidance authors concluded that the evidence base for IHC4 is currently limited to clinical validity (prognostic ability), although this evidence is considered to be relatively robust.

### *Mammostrat®*

The guidance authors did not identify any specific studies on the analytical validity of Mammostrat®, although some limited evidence on analytical validity was reported in studies of clinical validity and clinical utility. Three studies were identified that provided data to support the use of Mammostrat® as an independent prognostic tool for women with ER+, tamoxifen-treated breast ceancer. Although the evidence base for Mammostrat® is at present relatively limited, these studies included a large sample size and appeared to be of reasonable quality. No prospective studies of the impact of Mammostrat on long-term outcomes such as overall survival were identified. Clinical utility data on Mammostrat® from 1 study suggests that the low- and high-risk groups benefit from chemotherapy, but not the intermediate-risk group. There was no published evidence on reclassification of risk groups compared with conventional means of risk classification, and no evidence on the impact of the test on clinical decision-making.

### *Recommendations*

Oncotype DX® is recommended as an option for guiding adjuvant chemotherapy decisions for people with oestrogen receptor positive (ER+), lymph node negative (LN−) and human epidermal growth factor receptor 2 negative (HER2−) early breast cancer if:

- The person is assessed as being at intermediate risk and information on the biological features of the cancer provided by Oncotype DX® is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy and

- The manufacturer provides Oncotype DX® to NHS organizations according to the confidential arrangement agreed with NICE.
- The analysis leading to this recommendation was based on intermediate risk of distant recurrence being defined as a NPI score above 3.4. It is anticipated that an NPI score can be simply calculated from information that is routinely collected about people with breast cancer. Other decision-making tools or protocols are also currently used in the NHS and these may also be used to identify people at intermediate risk.
- MammaPrint®, IHC4, and Mammostrat® are only recommended for use in research in people with ER+, LN− and HER2− early breast cancer, to collect evidence about potentially important clinical outcomes and to determine the ability of the tests to predict the benefit of chemotherapy. The tests are not recommended for general use in these people because of uncertainty about their overall clinical benefit and consequently their cost effectiveness.

## CADTH (2014): Oncotype DX in Women and Men with ER-Positive, HER2-Negative Early Stage Breast Cancer who are either Lymph Node Negative or Lymph Node Positivee

### *Lymph Node Negative Disease*

The evidence base for the use of Oncotype DX® in women with ER+ HER2- LN- early stage breast cancer to eguide adjuvant chemotherapy treatment decisions includes four recent examples of secondary research (health technology assessments and systematic reviews) and four additional priemary studies. There is no evidence related specifically to men. Results consistently show about 30% of treatment plans are affected, primarily being lower rates of adjuvant chemotherapy for patients determined to be at low recurrence risk. For a smaller proportion determined to be at higher risk, adjuvant chemotherapy is suggested where initial treatment planning did not include it. The most uncertainty relates to the intermediate risk category where evidence is unclear; a large 7-country study (TAILORx) is focusing on the treatment of this group with study completion planned for late 2017.

### *Lymph Node Positive Disease*

A single UK National Institute for Health Research (NIHR) health technology assessment (HTA) by Ward et al. published in October 2013, which reviewed nine gene expression profiling and expanded immunohistochemistry tests used in the adjuvant treatment setting of breast cancer was included in this review. In addition to identifying new evidence, Ward et al. summarized two previous systematic reviews on the topic by Marchionni et al. (all LN- studies) and Smartt. (mix of LN- and LN+ studies). A total of three trials from the HTA were identified that looked at the LN+ population in isolation; the remainder of the evidence applied to the LN- or the undifferentiated (LN-/LN+) population. Smartt included a nested case control study by Goldstein et al. (n=465, LN-/LN+; 1-3 nodes: 43.6%) which examined clinical validity; in the subgroup of LN+ patients, Oncotype DX was found to better predict relapse at 5 years in chemotherapy/hormonal therapy-treated patients than usual clinical features. Two other retrospective cohort studies were identified by Ward et al. Dowsett et al. (n=1231, LN-/LN+;

LN+: 25%) also examined clinical validity in the subgroup of LN+ patients and found that the Oncotype DX recurrence score was significantly associated with time to distant recurrence (HR 3.47, 95% CI 1.64 to 7.38; $P < 0.002$). Albain et al. looked at clinical utility in an exclusively LN+ population. RS was found to be prognostic in the tamoxifen alone group (HR 2.64, 95% CI 1.33 to 5.27; $p = 0.006$); there was no benefit of chemotherapy found with a low RS, but improved disease-free survival when RS was high (adjusted HR 0.59, 95% CI 0.35 to 1.01; $P = 0.033$).

In summary, the clinical effectiveness of Oncotype DX®, as defined by its clinical validity and clinical utility in the population of early invasive breast cancer that is ER+, HER2-, and LN+, remains uncertain aes only three trials were identified, and they are limited by their retrospective designs.

## BCBS (2014). Gene Expression Analysis for Prostate Cancer Management.

### *Evidence overview: Prostate Cancer*

#### *Clinical background*

Prostate cancer is the second most common cancer diagnosed among men in the U.S. According to the National Cancer Institute, nearly 240,000 new cases are expected to be ediagnosed in the U.S. in 2013, associated with around 30,000 deaths. Localized prostate cancers meay appear clinically very similar at diagnosis. However, they often exhibit diverse risk of progression that may not be captured by accepted clinical risk categories (e.g., D'Amico criteria) or prognostic tools that are based on clinical findings, including prostate-specific antigen (PSA) titers, Gleason grade, or tumor stage. This creates uncertainty whether or not to treat immediately. A patient may choose definitive treatment comprising radiotherapy, surgery, chemotherapy, or androgen deprivation. Alternatively, the patient may forgo immediate therapy and continue regular monitoring until signs or symptoms of disease progression are evident, at which point curative treatment is instituted. This approach is referred to as "active surveillance." Given the unpredictable behavior of early prostate cancer, additional prognostic tests are under investigation. These include gene expression profiling using RTPCR-based technology. Gene expression profiling refers to analysis of mRNA expression levels of many genes simultaneously in a tumor specimen.

#### *Technology description*

Two gene expression profiling tests are now offered, intended to biologically stratify prostate cancers: Prolaris® (Myriad Genetices, Salt Lake City, UT) and Oncotype Dx® Prostate Cancer Assay (Genomic Health, Redwood City, CA). Both use archived tumor specimens as the mRNA source, reverse transcriptase polymerase chain reaction amplification, and a low density RTPCR array platform. Prolaris® is used to quantify expression levels of 31 cell cycle progression (CCP) genes and 15 housekeeper genes to generate a CCP score. Oncotype Dx® Prostate is used to quantify expression levels of 12 cancer-related and 5 reference genes to generate a Genomic Prostate Score (GPS). In the final analysis, the CCP score (median 1.03, interquartile range 0.41–1.74) and GPS (range 0–100) are combined in proprietary algorithms with clinical risk criteria (PSA, Gleason grade, tumor stage) to generate new risk categories (e.g., recelassification) intended to reflect biological indolence or aggressiveness of individual lesions, and thus inform management decisions.

### *Evidence review*

The review sought to answer the primary question: what is the incremental value of gene expression tests for discriminating men with aggressive and indolent disease to guide treatment decisions that improve net health outcomes?

### *Analytic Validity*

No specific information on the analytic validity of Prolaris® or Oncotype Dx® Prostate in the peer-reviewed literature, through an Internet search for grey literature, or on the developers' websites was identified. The FDA website does not contain specific information on either test.

### *Clinical Validity*

#### Prolaris®

One retrospective validation study on Prolaris® is based on patients (n=349) culled from 6 cancer registries in Great Britain. The study was designed to examine the clinical validity of the test showing association between a CCP gene expression score combined with clinical risk factors (PSA, Gleason score), and risk of prostate cancer death at 10 years post-diagnosis. The test was performed using micro-dissected tissue prepared from archived tumor specimens obtained through needle biopsy. A primary univariate analysis suggests that a 1-unit increase in CCP score was associated with a 2-fold increase in the hazard ratio for death from prostate cancer (hazard ratio=2.02, 95% confidence interval: 1.62 to 2.53, $p<10\text{-}9$). Three other studies of the Prolaris® CCP gene expression test were identified. Two used archived pathological specimens obtained from patients who underwent radical prostatectomy or transurethral resection of the prostate. The role of CCP analysis in those studies was to prognosticate for biochemical recurrence or prostate-specific mortality following treatment or watchful waiting, respectively. A third study reported results of CCP analysis as adjunct to clinical criteria to predict biochemical recurrence in men who underwent external-beam radiotherapy. The patients and management approaches in these studies do not represent the population of interest or address the primary question asked in this review.

#### Oncotype Dx® Prostate

No full-length peer-reviewed publications on the Oncotype Dx® Prostate test were identified. The developer's website contains information on a validation study to evaluate this test in needle biopsy specimens in a cohort of men in the United States. This study was presented at the 2013 annual meeting of the American Urological Association and had not been published. It evaluated the test in men who could be considered for active surveillance, and who would be representative of patients in contemporary practice. They report that a combination of the GPS from the test and clinical findings (e.g., PSA level, Gleason score) identified patients in specific risk categories and allowed reclassification between groupings as shown in Table 1. However, the number of patients correctly or incorrectly classified between all three categories cannot be ascertained.

### Table 1. Reclassification of Prostate Cancer Risk Categories With Oncotype Dx® Prostate

| NCCN Risk Level | Number of Patients Using Clinical Assessment (%) | Number of Patients Using GPS Plus Clinical Assessment (%) |
|---|---|---|
| **Very low** | 37 (10) | 100 (26) |
| **Low** | 191 (49) | 119 (31) |
| **Intermediate** | 160 (41) | 169 (44) |

#### *Clinical Utility*

No published evidence on the clinical utility of the Prolaris® or Oncotype Dx® Prostate test was identified. In summary, direct evidence is insufficient to establish the analytic validity, clinical validity, or clinical utility of either test.

## Evidence overview: Other Cancers

### AHRQ (2014): Prognosis in Multiple Cancers

#### *Clinical background*

Molecular pathology tests that identify pathogenic mutations and cytogenetic translocations help define the molecular subtypes of common cancers. Because several of these acquired mutations/translocations may predict response to specific therapies, screening tests for "targetable" mutations are now commonly available. It is unclear whether these test results can also serve as independent prognostic factors. This review aims to clarify the value of certain molecular pathology tests for improving estimates of prognosis for common cancers (breast, lung, colon, urinary bladder). The main purpose of this review is to determine whether these tests improve estimation of prognosis (for recurrence), affect physician decision making, and/or improve clinical outcomes when compared with traditional assessment of prognosis of recurrence. These genetic tests are used in two different contexts. In one, the tests are used in a specific context of a diagnostic/therapy combination, where the diagnostic test is being used to predict response to a very specific treatment. In the second context, the genetic tests are used to estimate the patient's prognosis, and physicians use this prognostic information to choose from a variety of different treatment options. This report evaluates the second context. Therefore, studies that evaluate specific diagnostic/therapy combinations are excluded from this report.

The following tests are under consideration for this assessment: microsatellite instability (MSI) for colorectal cancer (CRC), MLH1 promoter methylation for CRC, KRAS mutations for CRC, BRAF mutations for CRC, Oncotype DX Colon® mRNA expression for CRC, Oncotype DX Breast® mRNA expression for breast cancer, MammaPrint® mRNA expression for breast cancer, ALK cytogenetics for lung cancer, EGFR mutations for lung cancer, KRAS mutations for lung cancer, and UroVysion cytogenetics for urinary bladder cancer.

### *Evidence review*

No studies directly addressed the overarching question of whether the addition of the specified molecular pathology tests used alone or in combination with traditional prognostic factors changes physician decision making and improves outcomes. In addition, no studies addressed whether modified decisions lead to improved health outcomes.

### *Analytic Validity*

Included studies provide some evidence regarding analytic validity for all of the included tests. Data from included studies was supplemented with proficiency tests results provided by the College of American Pathologists (CAP) for five tests for which this data was available. Data on intra- and interlab reproducibility is available in the primary literature and through national organization proficiency testing programs. The College of American Pathologists sends proficiency test unknowns to CLIA-approved US clinical laboratories or International clinical laboratories, an excellent mechanism for assessing nationwide interlab reproducibility. The three most recent surveys for each of these analytes showed average accuracy rates of 95% for EGFR, 98% for KRAS, 99% for BRAF, 99% for MSI, and 99% for UroVysion™.

### *Clinical Validity*

Included studies provided some evidence on clinical validity for nine of the included tests, adjusted for known prognostic factors (Table 2). Evidence from multiple studies supports clinical validity, with added value beyond traditional prognostic factors, for MammaPrint®, Oncotype DX Breast®, KRAS mutation testing for lung cancer, BRAF mutation testing for CRC, KRAS mutation testing for CRC, and MSI for CRC for at least one outcome [risk of recurrence (RR), cancer-specific survival (CSS), or overall survival (OS)]. For UroVysion™, limited evidence from 2 small studies (total N=168) rated as low or medium risk of bias supported prognostic value for RR. EGFR lung cancer did not add prognostic value to the traditional factors used to determine prognosis. For CRC, evidence did not adequately support added prognostic value for Oncotype DX Colon®. The metric used to assess the clinical validity of the test for recurrence, CSS, or OS in all of these studies was the hazard ratio (HR), which in this report range from 0.57 to 3.93. If the test is non-informative, it would be expected that the probability of experiencing the end point would be the same for either group, with a HR of 1. If the HR is greater than 1, the probability of the endpoint is higher in the group with the higher hazard. If the HR is lower than 1, the probability of experiencing the endpoint is lower in the group with the lower hazard. For example, an HR of 2 for CSS indicates that one group (e.g., those with high risk results for Oncotype DX Breast®) has twice the rate per unit of time as the comparison group (e.g., those with low-risk test results).

### Table 2. Summary of Findings on Clinical Validity

| Test: Cancer | Outcome | N studies/ N subjects | Results (95% Confidence Interval) |
|---|---|---|---|
| MammaPrint®: Breast | RR | 6/1913 | HR: 2.84 (2.11 to 3.89) for poor prognosis vs. good prognosis |

| | | | |
|---|---|---|---|
| | CSS | 5/1615 | HR: 3.3 (2.22 to 4.9) for poor prognosis vs. good prognosis |
| | OS | 1/144 | HR: 1.67 (0.73 to 3.82) for poor prognosis vs. good prognosis |
| Oncotype DX®: Breast | RR | 6/3222 | HR: 2.97 (2.19 to 4.02) for high risk vs. low risk |
| | CSS | 2/1234 | HR: 2.02 (1.35 to 3.00) for high risk vs. low risk |
| | OS | 1/668 | HR: 1.65 (1.24 to 2.19) for high risk vs. low risk |
| EGFR: Lung | RR | 6/1870 | HR: 0.87 (0.65 to 1.15); No association |
| | CSS | 0 | N/A |
| | OS | 6/ 1820 | HR: 0.76 (0.50 to 1.19); No association |
| KRAS: Lung | RR | 4/611 | 2.84 (1.14 to 7.1) KRAS mutation associated with greater RR |
| | CSS | 0 | N/A |
| | OS | 2/253 | 2.69 (1.91 to 3.8); 3.33 (1.03 to 10.82) |
| BRAF: CRC | RR | 5/4106 | HR 1.07 (0.76 to 1.52) for wild-type vs. mutation |
| | CSS | 7/5409 | HR 1.50 (1.26 to 1.77) for wild-type vs. mutation |
| | OS | 11/7610 | HR 1.45 (1.29 to 1.62) for wild-type vs. mutation |
| KRAS: CRC | RR | 5/4085 | HR 1.02 (0.91 to 1.14) for wild-type vs. mutation |
| | CSS | 2/1174 | HR 1.30 (1.02 to 1.66) for wild-type vs. mutation |
| | OS | 10/5328 | HR 1.22 (0.93 to 1.60) for wild-type vs. mutation |
| MSI: CRC | RR | 10/7130 | HR 0.60 (0.50 to 0.72) for MSI-H vs. MSS |
| | CSS | 6/3439 | HR 0.65 (0.51 to 0.82) for MSI-H vs. MSS |
| | OS | 12/8839 | HR 0.57 (0.43 to 0.77) for MSI-H vs. MSS |
| Oncotype DX®: CRC | RR | 1/690 | HR 1.68 (1.18 to 2.38) |
| | CSS | 0 | N/A |
| | OS | 0 | N/A |
| UroVysion™: Bladder | eRR | 2/168 | Association between mutation and RR in 2 small studies |
| | CSS | 0 | N/A |
| | OS | 0 | N/A |

### *Clinical Utility*

The evidence was insufficient to answer the overarching question for most tests. Even in the cases where the tests seemed to add value in determining prognosis (e.g., evidence of clinical validity), no evidence was identified that suggested using the test was related to improved outcomes for patients. For a few tests (EGFR for lung cancer, BRAF for colorectal cancer and KRAS for colorectal cancer), there was low SOE suggesting that using the test would not improve outcomes for patients, since if there is a lack of clinical validity, it is unlikely that the tests will be found to have clinical utility. For impact on treatment decisions, there was moderate SOE that one test, Oncotype DX Breast®, leads to changes in decisions. Although the decision changes were observed in both directions for individual patients, studies consistently showed an overall shift to less-intensive treatment recommendations as a result of using Oncotype DX Breast®, with fewer recommendations for chemotherapy. In these situations, there is less exposure to potential harms of chemotherapy, however, the studies did not follow patients to actually report on harms or to assess the overall balance of clinical benefits and harms. One study of low or medium risk of bias was found for the impact of MammaPrint® on treatment decisions; the authors concluded that evidence was insufficient to determine the impact of MammaPrint® on treatment decisions, primarily because of unknown consistency and imprecision.

## BCBS (2013): Multiple Molecular Testing of Cancers to Identify Targeted Therapies

### *Clinical Background*

Measurement of genetic or other molecular markers in cancer tissue is established in the deiagnosis, staging, and treatment of cancer. Currently, there is interest in the utility of measuring a large number of molecular markers at a single time in order to identify a treatment which targets the biological pathway involving that molecular marker. The available methods, or assays, may include molecular markers that individually might be indicated for a specific cancer, but are not indicated for most cancers. This may result in a different treatment than usually selected for a patient based on the type of cancer and its stage.

The use of multiple molecular testing to select targeted therapy is based on a shift in thinking about cancer behavior and treatment. Rather than thinking about cancer based on site and histology, molecular markers represent biological pathways that may be common across cancers. Choosing treatment based on these biological pathways is hypothesized to be a better method of selecting treatment.

Use of multiple molecular markers to select treatment can generally be categorized in two ways. Performing a large number of tests might increase the probability of a positive test, which indicates possible susceptibility of the cancer to a targeted therapy usually not indicated for that particular cancer. Alternatively, the results of large numbers of tests might be integrated in some manner to construct an interlinked biologic pathway for that particular cancer, thereby providing insight into a potentially more effective targeted therapy for that particular patient.

A variety of techniques are used to profile cancers. Several of the commercially available panels combine different techniques. Some provide highly related or what might be considered redundant information regarding the tumor. Because of rapid changes in technology and the development of novel methods, the actual technique employed may be less relevant than the nature of the information derived from the test. Some types of information such as presence of specific mutations can be obtained from several different techniques. The authors state that it is beyond the scope of their report to detail the many different panels that are commercially available at the time the report was written. This report also does not evaluate the use of multiple molecular testing in the setting where such tests have been selected and combined in a specific computational model to create a single "test" used for prognosis or treatment selection, such as Oncotype DX.

### *Evidence Review*

Three published studies, including a variety of cancers (breast, colon, ovarian, melanoma, thyroid, miscellaneous) report health outcomes for patients whose treatments were selected using multiple molecular marker panels. Two of the studies compare the time to progression on the targeted treatment to the time to progression on the most recently failed treatment. This is not an established measure of efficacy or treatment response. One study compares patients who had targeted treatment to another group of patients who did not have targeted treatment. This study was not randomized and thus may be subject to confounding. In two of the studies, subjects were given targeted treatments in Phase I trials. Outcomes of these patients could be dependent on the experimental treatment rather than the selection strategy. In summary, use of multiple molecular testing to assist in making treatment decisions for cancer patients is rapidly evolving. Strong evidence of clinical effectiveness of this approach is not available, and a number of issues remain to be solved, particularly patient selection.

### *Evidence for BRAF testing in melanoma*

A Special Report published by BCBS in 2011 investigated the targeted drug design and companion test co-development of vemurafenib (a BRAF inhibitor that targets a mutated form of the BRAF kinase) and the cobas® 4800 BRAF V600 Mutation Test real-time polymerase chain reaction (PCR) test. The primary evidence of clinical validity and utility for the cobas 4800 BRAF V600 Mutation Test is provided by the Phase III clinical trial of vemurafenib, which also supported the FDA approval of the drug.

The Phase I single-arm clinical trial of vemurafenib used a prototype assay to detect BRAFV600E mutations in enrolled patients. After dose determination, the extension phase of the study resulted in 81% of 32 patients responding according to Response Evaluation Criteria in Solid Tumors (RECIST); nearly all were partial responses. The Phase II single-arm clinical trial is currently ongoing; interim results presented at a meeting showed a 53% objective response rate, median progression-free survival of 6.7 months, and median overall survival not reached at the time of analysis. Patients were selected for enrollment based on a finalized version of the cobas 4800 BRAF V600 Mutation Test.

The Phase III comparative trial of vemurafenib versus standard chemotherapy (dacarbazine) also enrolled patients based on the results of the finalized companion test. At a planned interim

analysis, the results met the specified criteria for primary endpoints, and patients in the dacarbazine treatment arm were allowed to cross over to vemurafenib. At this time, median survival had not been reached; the hazard ratio for death was 0.37 (95% CI: 0.26–0.55). At 6 months, overall survival was 84% (95% CI: 78 to 89) for vemurafenib-treated patients and 64% (95% CI: 56 to 73) for dacarbazine-treated patients. Progression-free survival was evaluable in 549 patients; the hazard ratio for tumor progression was 0.26 (95% CI: 0.20–0.33). The median progression-free survival was estimated to be 5.3 months for patients treated with vemurafenib and 1.6 months for patients treated with dacarbazine. Tumor response was evaluable in 439 patients; the objective response rate was 48% in patients treated with vemurafenib versus 5% in those treated with dacarbazine. Only 2 patients treated with vemurafenib had a complete response.

Extended follow-up of this trial was published in 2014 by McArthur and colleagues. Median overall survival was significantly longer in the vemurafenib group than in the dacarbazine group (13.6 months [95% CI 12.0–15.2] vs 9.7 months [7.9–12.8]; hazard ratio [HR] 0.70 [95% CI 0.57–0.87]; p=0.0008), as was median progression-free survival (6.9 months [95% CI 6.1–7.0] vs 1.6 months [1.6–2.1]; HR 0.38 [95% CI 0.32–0.46]; p<0.0001). For the 598 (91%) patients with *BRAF* $V600^{E}$ disease, median overall survival in the vemurafenib group was 13.3 months (95% CI 11.9–14.9) compared with 10.0 months (8.0–14.0) in the dacarbazine group (HR 0.75 [95% CI 0.60–0.93]; p=0.0085); median progression-free survival was 6.9 months (95% CI 6.2–7.0) and 1.6 months (1.6–2.1), respectively (HR 0.39 [95% CI 0.33–0.47]; p<0.0001). For the 57 (9%) patients with the more uncommon *BRAF* $V600^{K}$ disease, median overall survival in the vemurafenib group was 14.5 months (95% CI 11.2–not estimable) compared with 7.6 months (6.1–16.6) in the dacarbazine group (HR 0.43 [95% CI 0.21–0.90]; p=0.024); median progression-free survival was 5.9 months (95% CI 4.4–9.0) and 1.7 months (1.4–2.9), respectively (HR 0.30 [95% CI 0.16–0.56]; p<0.0001). The most frequent grade 3–4 events were cutaneous squamous-cell carcinoma (65 [19%] of 337 patients) and keratoacanthomas (34 [10%]), rash (30 [9%]), and abnormal liver function tests (38 [11%]) in the vemurafenib group and neutropenia (26 [9%] of 287 patients) in the dacarbazine group. Eight (2%) patients in the vemurafenib group and seven (2%) in the dacarbazine group had grade 5 events.

The results of the Phase III trial, supported by the results of the earlier trials, support the clinical validity and clinical utility of the cobas 4800 BRAF V600 Mutation Test, the companion diagnostic test for vemurafenib. Using the test to select patients for treatment results in improved outcomes compared to the usual standard of care, dacarbazine. In addition, comparison of these results with the trial results of the recently approved ipilimumab, suggests that treatment with vemurafenib results in improved outcomes compared to ipilimumab. Ipilimumab is notable as the first therapy to show a survival advantage in a Phase III trial for patients with advanced melanoma, and while vemurafenib was in clinical trials, may have become the new treatment standard for late stage disease and thus is an important comparator.

### *Evidence for EGFR testing in lung cancer*

The 2014 AHRQ report referenced above concluded that “EGFR lung cancer did not add prognostic value to the traditional factors used to determine prognosis.” However, other authors have drawn different conclusions. A diagnostics guidance from NICE (2013) concluded that

epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing is indicated in adults with previously untreated, locally advanced or metastatic non-small-cell lung cancer (NSCLC). Clinical trials have shown that patients with EGFR-TK mutation-positive tumours gain more benefit from treatment with EGFR-TK inhibitors than from standard chemotherapy treatment. Conversely, patients with EGFR-TK mutation-negative tumours gain more benefit from standard chemotherapy than from EGFR-TK inhibitors. However, there was no consensus on which laboratory test should be used for clinical decision-making.

A clinical effectiveness review by CADTH (Mujoomdar 2010) concluded that PCR-based tests are likely useful for identifying patients with NSCLC who are likely to respond to treatment with a TKI, and notes that in December 2009, Health Canada approved the TKI gefitinib as a first-line treatment for patients with locally advanced or metastatic NSCLC who also have activating mutations in the EGFR gene.

### *Evidence for KRAS testing in colorectal cancer*

The 2014 AHRQ report concluded that there was low SOE suggesting that using this test would not improve outcomes for patients, since if there is a lack of clinical validity, it is unlikely that the tests will be found to have clinical utility. Other authors have suggested that, although testing may not improve mortality in colorectal cancer, it may save patients from unnecessary treatment by identifying those who are unlikely to benefit from anti-epidermal growth factor receptor monoclonal antibody therapy. A 2010 AHRQ report on selected pharmacogenetic tests for cancer treatment (Terasawa 2010) included 47 eligible studies and concluded that when treated with anti-EGFR antibodies, patients with KRAS mutations were less likely to experience treatment benefit, compared to patients whose tumors were wild-type for KRAS mutations, for all outcomes assessed. These results were confirmed in several RCT-based analyses of progression-free survival that demonstrated a significant treatment-by-KRAS mutation interaction in three out of the four cases where such analyses were reported. The direction of effect was consistent among studies, and formal significance was achieved in the majority of individual studies that reported information on the clinically relevant outcomes of overall and disease-free survival.

A working group convened by Evaluation of Genomic Applications in Practice and Prevention (EGAPP) found that, for patients with metastatic colorectal cancer who are being considered for treatment with cetuximab or panitumumab, there is convincing evidence to recommend clinical use of KRAS mutation analysis to determine which patients are KRAS mutation positive and therefore unlikely to benefit from these agents before initiation of therapy. The level of certainty of the evidence was deemed high, and the magnitude of net health benefit from avoiding potentially ineffective and harmful treatment, along with promoting more immediate access to what could be the next most effective treatment, is at least moderate.

## EVIDENCE SUMMARY

For breast cancer, there is moderate quality evidence that Oncotype DX® has adequate analytic validity, clinical validity and clinical utility, at least in intermediate risk women. A similar statement cannot be made for the other gene profiling tests: Mammaprint® has reasonable

evidence of clinical validity but insufficient evidence pertaining to clinical utility. The evidence base for IHC4 is limited to clinical validity (no evidence on analytic validity or clinical utility). For Mammostrat®, evidence from three studies suggests adequate clinical validity, however evidence on clinical utility is limited to one study, and is considered insufficient.

This evidence primarily pertains to women with lymph node negative breast cancer. The evidence for lymph node positive cancer is limited to Oncotype DX®, for which only 3 studies were identified, and clinical utility is uncertain.

For prostate cancer, there is no analytic validity or clinical utility evidence for either approved test. Evidence on the clinical validity is also quite limited for both tests.

For other cancers, AHRQ 2014 found insufficient evidence to suggest that use of any evaluated gene profiling test would result in improved outcomes for patients; but concluded that a low strength of evidence supports that the following tests would not be useful, since they did not demonstrate clinical validity: EGFR for lung cancer, BRAF for colorectal cancer and KRAS for colorectal cancer.

However, other authors have reached different conclusions on EGFR for lung cancer and KRAS for colorectal cancer. Lung cancer patients with wild-type EGFR-TK are more likely to benefit from standard chemotherapy, while patients with mutated EGFR-TK are more likely to respond to targeted gene inhibitors. Colorectal cancer patients with KRAS mutations are unlikely to benefit from with anti-EGFR antibodies such as cetuximab or panitumumab. BRAF testing to select melanoma patients for treatment with a targeted BRAF inhibitor results in improved outcomes compared to the usual standard of care, according to results of a Phase III trial.

There is insufficient evidence of clinical effectiveness pertaining to the use of multiple molecular testing to select targeted therapy in a variety of cancers.

## 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 |
|---|---|---|---|---|---|---|
| Oncotype DX® (lymph node - breast) | Change in treatment decision in ~1/3rd of patients | Moderate# | Low | Moderate variability | Recommended for coverage *(strong recommendation)* | Sufficient evidence, more effective, less harms. (IA1b) |
| Oncotype DX® (lymph node + breast) | Some evidence of clinical validity and utility | Low# | Low | Moderate variability | Do not recommend (*weak recommendation*) | Evidence insufficient, less risk, equal or more cost. Expert opinion indicates women with lymph positive breast cancer receive chemotherapy regardless of test results. (IIA1a) |
| Mammaprint® (breast) | Unknown | Very low# | Unknown | Low variability | Do not recommend (*weak recommendation*) | Evidence insufficient; available alternatives but risk comparison is |

| Indication/ Intervention | Balance between desirable and undesirable effects | Quality of evidence*# | Resource allocation | Variability in values and preferences | Coverage recommendation | Rationale |
|---|---|---|---|---|---|---|
| | | | | | | unknown (IIA3) |
| IHC4 (breast) | Unknown | Very low# | Unknowen | Low variability | Do not recommend (*weak recommendation*) | Evidence insufficient; available alternatives but risk comparison is unknown (IIA3) |
| Mammostrat® (breast) | Unknown | Very low# | Unknown | Low variability | Do not recommend (*weak recommendation*) | Evidence insufficient; available alternatives but risk comparison is unknown (IIA3) |
| Prolaris®/ Oncotype DX® (prostate) | Unknown | Very low* | Unknown | Low variability | Do not recommend (*weak recommendation*) | Evidence insufficient; available alternatives but risk comparison is unknown (IIA3) |
| EGFR (Lung) | Some evidence of clinical validity and utility | Low* | Unknown | Low variability | Recommend strong | Sufficient evidence, more effective, less harms. (IA1b) |
| KRAS (Lung) | Unknown | Very low* | Unknown | Low variability | Do not recommend (*weak recommendation*) | Evidence insufficient; available alternatives but risk comparison is unknown (IIA3) |
| BRAF (CRC) | No clinical validity | Low* | Unknown | Low variability | Do not recommend (*strong recommendation*) | Sufficient evidence, ineffective or benefit exceeds harms. (IA4) |
| KRAS (CRC) | Some evidence of clinical validity | Low* | Unknown | Low variability | Recommended for coverage (*strong* | Sufficient evidence, more effective, less |

| Indication/ Intervention | Balance between desirable and undesirable effects | Quality of evidence*# | Resource allocation | Variability in values and preferences | Coverage recommendation | Rationale |
|---|---|---|---|---|---|---|
| | and utility | | | | *recommendation*) | harms. (IA1b) |
| MSI (CRC) | Unknown | Very low* | Unknown | Low variability | Do not recommend (*weak recommendation*) | Evidence insufficient; available alternatives but risk comparison is unknown IIA3 |
| Oncotype DX® (CRC) | Unknown | Very low* | Unknown | Low variability | Do not recommend (*weak recommendation*) | Evidence insufficient; available alternatives but risk comparison is unknown IIA3 |
| UroVysion™ (Bladder) | Unknown | Very low* | Moderate | Low variability | Do not recommend (*weak recommendation*) | Evidence insufficient; available alternatives but risk comparison is unknown IIA3 |
| BRAF (melanoma) | Some evidence of clinical validity and utility | Very low | Unknown | Low variability | Recommended for coverage (*strong recommendation*) | Sufficient evidence, more effective, less harms. (IA1b) |

*The Quality of Evidence rating was assigned by the primary evidence source

#The Quality of Evidence rating was assigned by the HERC Subcommittee

Note: GRADE framework elements are described in Appendix A.

# POLICY LANDSCAPE

## Quality measures

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

## PROFESSIONAL SOCIETY GUIDELINES

The National Comprehensive Cancer Network produced a Task Force report pertaining to the clinical utility of tumor markers in oncology. For this report, they combined the Tumor Marker Utility Grading System (TMUGS) and the levels of evidence standards for using archived tissue to assess the level of evidence that supports a particular test. They are presented in the tables below:

### TABLE 3 TUMOR MARKER UTILITY GRADING SYSTEM

| Level of evidence | Definition/ Trial Design |
|---|---|
| I | Prospective, marker primary objective, well-powered or meta-analysis |
| II | Prospective, marker the secondary objective |
| III | Retrospective, outcomes, multivariate analysis |
| IV | Retrospective, outcomes, univariate analysis |
| V | Retrospective, correlation with other marker, no outcomes |

### TABLE 4 LEVELS OF EVIDENCE STANDARDS FOR USING ARCHIVED TISSUE TO ASSESS THE LEVEL OF EVIDENCE THAT SUPPORTS A PARTICULAR TEST

| Level of Evidence Category | Trial design required to determine clinical validity |
|---|---|
| A | Prospective, designed to address tumor marker |
| B | Prospective using archived samples (not designed to address tumor marker, but can accommodate) |
| C | Prospective observational registry (treatment and follow up not dictated) |
| D | Retrospective observational |

In addition, the NCCN uses categories of evidence and consensus, outlined in Table 5:

### TABLE 5 NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

| Category | Definition |
|---|---|
| **1** | Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **2A** | Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **2B** | Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. |
| **3** | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

For the cancers considered in this coverage guidance document, the NCCN lists levels and categories of evidence for selected tumor markers. These are outlined in Table 6.

### TABLE 6 TUMOR MARKERS FOR SELECTED CANCERS WITH ACCEPTED CLINICAL UTILITY

| Cancer | Tumor Marker | Level of Evidence | Category of Evidence |
|---|---|---|---|
| Breast | ER/PR | IB | 2A |
| | HER2 | IA | 2A |
| | Oncotype DX | Prognostic: IB<br>Predictive: IIA | 2A/ 2B |
| | KRAS mutations | Predictive: IB<br>Prognostic: IIB | 2A |
| Colon | MSI and/or MMR protein loss | Screening: IB<br>Prognostic: IB<br>Predictive: IIB | 2A |
| | CEACAM5 | IIC | 2A |
| | BRAF c. 1799T>A | Prognostic: IB<br>Predictive: IIIC | 2A |
| | EGFR mutation | IA | 1 |
| Non-Small Cell Lung Cancer | ALK gene fusion | IIB | 2A |
| | PSA (KLK3) | IA | 2A |
| Prostate | | | |

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

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

# APPENDIX A. GRADE ELEMENT DESCRIPTIONS

| Element | Description |
|---|---|
| Balance between desirable and undesirable effects | The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted |
| Quality of evidence | The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted |
| Resource allocation | The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted |
| Values and preferences | The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted |

## Strong recommendation

***In Favor:*** The subcommittee is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.
***Against:*** The subcommittee is confident that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences.

## Weak recommendation

***In Favor:*** The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.
***Against:*** The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the quality of evidence, cost and resource allocation, and values and preferences, but is not confident.

## Quality or strength of evidence rating across studies for the treatment/outcome[1]

***High:*** The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.
***Moderate:*** The subcommittee is moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
***Low***: The subcommittee's confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
***Very low***: The subcommittee has very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

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

# APPENDIX B. APPLICABLE CODES

| CODES | DESCRIPTION |
|---|---|
| **ICD-9 Diagnosis Codes** | |
| 153.0 | Malignant neoplasm of hepatic flexure |
| 153.1 | Malignant neoplasm of transverse colon |
| 153.2 | Malignant neoplasm of descending colon |
| 153.3 | Malignant neoplasm of sigmoid colon |
| 153.4 | Malignant neoplasm of cecum |
| 153.5 | Malignant neoplasm of appendix vermiformis |
| 153.6 | Malignant neoplasm of ascending colon |
| 153.7 | Malignant neoplasm of splenic flexure |
| 153.8 | Malignant neoplasm of other specified sites of large intestine |
| 153.9 | Malignant neoplasm of colon unspecified site |
| 154.0 | Malignant neoplasm of rectosigmoid junction |
| 154.1 | Malignant neoplasm of rectum |
| 154.2 | Malignant neoplasm of anal canal |
| 154.3 | Malignant neoplasm of anus unspecified site |
| 154.8 | Malignant neoplasm of other sites of rectum rectosigmoid junction and anus |
| 162.2 | Malignant neoplasm of main bronchus |
| 162.3 | Malignant neoplasm of upper lobe bronchus or lung |
| 162.4 | Malignant neoplasm of middle lobe bronchus or lung |
| 162.5 | Malignant neoplasm of lower lobe bronchus or lung |
| 162.8 | Malignant neoplasm of other parts of bronchus or lung |
| 162.9 | Malignant neoplasm of bronchus and lung unspecified |
| 174.0 | Malignant neoplasm of nipple and areola of female breast |
| 174.1 | Malignant neoplasm of central portion of female breast |
| 174.2 | Malignant neoplasm of upper-inner quadrant of female breast |
| 174.3 | Malignant neoplasm of lower-inner quadrant of female breast |
| 174.4 | Malignant neoplasm of upper-outer quadrant of female breast |
| 174.5 | Malignant neoplasm of lower-outer quadrant of female breast |
| 174.6 | Malignant neoplasm of axillary tail of female breast |
| 174.8 | Malignant neoplasm of other specified sites of female breast |
| 174.9 | Malignant neoplasm of breast (female) unspecified site |
| 185 | Malignant neoplasm of prostate |
| 188.0 | Malignant neoplasm of trigone of urinary bladder |
| 188.1 | Malignant neoplasm of dome of urinary bladder |
| 188.2 | Malignant neoplasm of lateral wall of urinary bladder |
| 188.3 | Malignant neoplasm of anterior wall of urinary bladder |
| 188.4 | Malignant neoplasm of posterior wall of urinary bladder |
| 188.5 | Malignant neoplasm of bladder neck |
| 188.6 | Malignant neoplasm of ureteric orifice |
| 188.7 | Malignant neoplasm of urachus |

| | |
|---|---|
| 188.8 | Malignant neoplasm of other specified sites of bladder |
| 188.9 | Malignant neoplasm of bladder part unspecified |
| 196.0 | Secondary and unspecified malignant neoplasm of lymph nodes of head face and neck |
| 196.1 | Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes |
| 196.2 | Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes |
| 196.3 | Secondary and unspecified malignant neoplasm of lymph nodes of axilla and upper limb |
| 196.5 | Secondary and unspecified malignant neoplasm of lymph nodes of inguinal region and lower limb |
| 196.6 | Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes |
| 196.8 | Secondary and unspecified malignant neoplasm of lymph nodes of multiple sites |
| 196.9 | Secondary and unspecified malignant neoplasm of lymph nodes site unspecified |
| V07.51 | Use of selective estrogen receptor modulators (serms) |
| V07.52 | Use of aromatase inhibitors |
| V07.59 | Use of other agents affecting estrogen receptors and estrogen levels |
| V10.3 | Personal history of malignant neoplasm of breast |
| V58.11 | Encounter for antineoplastic chemotherapy |
| V84.01 | Genetic susceptibility to malignant neoplasm of breast |
| V86.0 | Estrogen receptor positive status [ER+] |
| V86.1 | Estrogen receptor negative status [ER-] |
| **ICD-10 Diagnosis Codes** | |
| C18.3 | Malignant neoplasm of hepatic flexure |
| C18.4 | Malignant neoplasm of transverse colon |
| C18.6 | Malignant neoplasm of descending colon |
| C18.7 | Malignant neoplasm of sigmoid colon |
| C18.0 | Malignant neoplasm of cecum |
| C18.1 | Malignant neoplasm of appendix |
| C18.2 | Malignant neoplasm of ascending colon |
| C18.5 | Malignant neoplasm of splenic flexure |
| C18.8 | Malignant neoplasm of overlapping sites of colon |
| C18.9 | Malignant neoplasm of colon, unspecified |
| C19 | Malignant neoplasm of rectosigmoid junction |
| C20 | Malignant neoplasm of rectum |
| C21.1 | Malignant neoplasm of anal canal |
| C21.0 | Malignant neoplasm of anus, unspecified |
| C21.8 | Malignant neoplasm of overlapping sites of rectum, anus and anal canal |
| C34.00 | Malignant neoplasm of unspecified main bronchus |
| C34.10 | Malignant neoplasm of upper lobe, unspecified bronchus or lung |
| C34.2 | Malignant neoplasm of middle lobe, bronchus or lung |
| C34.30 | Malignant neoplasm of lower lobe, unspecified bronchus or lung |
| C34.80 | Malignant neoplasm of overlapping sites of unspecified bronchus and lung |
| C34.90 | Malignant neoplasm of unspecified part of unspecified bronchus or lung |
| C50.019 | Malignant neoplasm of nipple and areola, unspecified female breast |
| C50.119 | Malignant neoplasm of central portion of unspecified female breast |

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| C50.219 | Malignant neoplasm of upper-inner quadrant of unspecified female breast |
| C50.319 | Malignant neoplasm of lower-inner quadrant of unspecified female breast |
| C50.419 | Malignant neoplasm of upper-outer quadrant of unspecified female breast |
| C50.519 | Malignant neoplasm of lower-outer quadrant of unspecified female breast |
| C50.619 | Malignant neoplasm of axillary tail of unspecified female breast |
| C50.819 | Malignant neoplasm of overlapping sites of unspecified female breast |
| C50.919 | Malignant neoplasm of unspecified site of unspecified female breast |
| C61 | Malignant neoplasm of prostate |
| C67.0 | Malignant neoplasm of trigone of bladder |
| C67.1 | Malignant neoplasm of dome of bladder |
| C67.2 | Malignant neoplasm of lateral wall of bladder |
| C67.3 | Malignant neoplasm of anterior wall of bladder |
| C67.4 | Malignant neoplasm of posterior wall of bladder |
| C67.5 | Malignant neoplasm of bladder neck |
| C67.6 | Malignant neoplasm of ureteric orifice |
| C67.7 | Malignant neoplasm of urachus |
| C67.8 | Malignant neoplasm of overlapping sites of bladder |
| C67.9 | Malignant neoplasm of bladder, unspecified |
| C77.0 | Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck |
| C77.1 | Secondary and unspecified malignant neoplasm of intrathoracic lymph nodes |
| C77.2 | Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes |
| C77.3 | Secondary and unspecified malignant neoplasm of axilla and upper limb lymph nodes |
| C77.4 | Secondary and unspecified malignant neoplasm of inguinal and lower limb lymph nodes |
| C77.5 | Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes |
| C77.8 | Secondary and unspecified malignant neoplasm of lymph nodes of multiple regions |
| C77.9 | Secondary and unspecified malignant neoplasm of lymph node, unspecified |
| Z79.810 | Long term (current) use of selective estrogen receptor modulators (SERMs) |
| Z79.811 | Long term (current) use of aromatase inhibitors |
| Z79.818 | Long term (current) use of other agents affecting estrogen receptors and estrogen levels |
| Z85.3 | Personal history of malignant neoplasm of breast |
| Z51.11 | Encounter for antineoplastic chemotherapy |
| Z15.01 | Genetic susceptibility to malignant neoplasm of breast |
| Z17.0 | Estrogen receptor positive status [ER+] |
| Z17.1 | Estrogen receptor negative status [ER-] |
| **ICD-9 Volume 3 (Procedure Codes)** | |
| 32 | Excision of lung and bronchus |
| 85.2 | Excision or destruction of breast tissue |
| 85.4 | Mastectomy |
| 45.7 | Open and other partial excision of large intestine |
| 45.8 | Total intra-abdominal colectomy |
| 45.9 | Intestinal anastomosis |
| 48.4 | Pull-through resection of rectum |
| 48.5 | Abdominoperineal resection of rectum |

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| 48.6 | Other resection of rectum |
| 57.4 | Transurethral excision or destruction of bladder tissue |
| 57.5 | Other excision or destruction of bladder tissue |
| 57.6 | Partial cystectomy |
| 57.7 | Total cystectomy |
| 60.5 | Radical prostatectomy |
| **CPT Codes** | |
| 19301 | Mastectomy, partial |
| 19302 | Mastectomy, with axillary lymphadenectomy |
| 19303 | Mastectomy, simple, complete |
| 19304 | Mastectomy, subcutaneous |
| 19305 | Mastectomy, radical, including pectoral muscles, axillary lymph nodes |
| 19306 | Mastectomy, radical, including pectoral muscles, axillary and internal mammary lymph nodes |
| 19307 | Mastectomy, modified radical, including axillary lymph nodes, with or without pectoralis minor muscle but excluding pectoralis major muscle |
| 32440 | Removal of lung, pneumonectomy |
| 32442 | Removal of lung, pneumonectomy; with resection of segment o trachea followed by broncho-tracheal anastomosis |
| 32445 | Removal of lung, pneumonectomy; extrapleural |
| 32480 | Removal of lung other than pneumonectomy; single lobe |
| 32482 | Removal of lung other than pneumonectomy; 2 lobes |
| 32484 | Removal of lung other than pneumonectomy; single segment |
| 32486 | Removal of lung other than pneumonectomy; with circumferential resection of segment of bronchus followed by broncho-bronchial anastomosis |
| 32488 | Removal of lung other than pneumonectomy; with all remaining lung following previous removal of a portion of lung |
| 32491 | Removal of lung other than pneumonectomy; with resection-plication of emphysematous lung(s) for lung volume reduction, sternal split or transthoracic approach, includes any pleural procedure, when preformed |
| 32501 | Resection and repair of portion of bronchus when performed at a time of lobectomy or segmentectomy |
| 32503 | Resection of apical lung tumor including chest wall resection, rib(s) resection(s), neurovascular dissection, when performed; without chest wall reconstruction(s) |
| 32504 | Resection of apical lung tumor including chest wall resection, rib(s) resection(s), neurovascular dissection, when performed; with chest wall reconstruction(s) |
| 44139 | Mobilization (take-down) of splenic flexure performed in conjunction with partial colectomy (List separately in addition to primary procedure) |
| 44140 | Colectomy, partial; with anastomosis |
| 44141 | Colectomy, partial; with skin level cecostomy or colostomy |
| 44143 | Colectomy, partial; with end colostomy and closure of distal segment (Hartmann type procedure) |
| 44144 | Colectomy, partial; with resection, with colostomy or ileostomy and creation of mucofistula |
| 44145 | Colectomy, partial; with coloproctostomy (low pelvic anastomosis) |
| 44146 | Colectomy, partial; with coloproctostomy (low pelvic anastomosis), with colostomy |
| 44147 | Colectomy, partial; abdominal and transanal approach |
| 44150 | Colectomy, total, abdominal, without proctectomy; with ileostomy or ileoproctostomy |
| 44151 | Colectomy, total, abdominal, without proctectomy; with continent ileostomy |

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| 44155 | Colectomy, total, abdominal, with proctectomy; with ileostomy |
| 44156 | Colectomy, total, abdominal, with proctectomy; with continent ileostomy |
| 44157 | Colectomy, total, abdominal, with proctectomy; with ileoanal anastomosis, includes loop ileostomy, and rectal muscosectomy, when performed |
| 44158 | Colectomy, total, abdominal, with proctectomy; with ileoanal anastomosis, creation of ileal reservoir (S or J), includes loop ileostomy, and rectal muscosectomy, when perfomed |
| 44160 | Colectomy, partial, with removal of terminal ileum with ileocolostomy |
| 51570 | Cystectomy, complete; (separate procedure) |
| 51575 | Cystectomy, complete; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes |
| 51580 | Cystectomy, complete, with ureterosigmoidostomy or ureterocutaneous transplantations; |
| 51585 | Cystectomy, complete, with ureterosigmoidostomy or ureterocutaneous transplantations; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes |
| 51590 | Cystectomy, complete, with ureteroileal conduit or sigmoid bladder, including intestine anastomosis; |
| 51595 | Cystectomy, complete, with ureteroileal conduit or sigmoid bladder, including intestine anastomosis; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes |
| 51596 | Cystectomy, complete, with continent diversion, any open technique, using any segment of small and/or large intestine to construct neobladder |
| 51597 | Pelvic exenteration, complete, for vesical, prostatic or urethral malignancy, with removal of bladder and ureteral transplantations, with or without hysterectomy and/or abdominoperineal resection of rectum and colon and colostomy, or any combination thereof |
| 55810 | Prostatectomy, perineal radical; |
| 55812 | Prostatectomy, perineal radical; with lymph node biopsy(s) (limited pelvic lymphadenectomy) |
| 55815 | Prostatectomy, perineal radical; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric and obturator nodes |
| 55821 | Prostatectomy (including control of postoperative bleeding, vasectomy, meatotomy, urethral calibration and/or dilation, and internal urethrotomy); suprapubic, subtotal, 1 or 2 stages |
| 55831 | Prostatectomy (including control of postoperative bleeding, vasectomy, meatotomy, urethral calibration and/or dilation, and internal urethrotomy); retropubic, subtotal |
| 55840 | Prostatectomy, retropubic radical, with or without nerve sparing |
| 55842 | Prostatectomy, retropubic radical, with or without nerve sparing; with lymph node biopsy(s) (limited pelvic lymphadenectomy) |
| 55842 | Prostatectomy, retropubic radical, with or without nerve sparing; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes |
| 55860 | Exposure of prostate, any approach, for insertion of radioactive substance |
| 55862 | Exposure of prostate, any approach, for insertion of radioactive substance; with lymph node biopsy(s) (limited pelvic lymphadenectomy) |
| 55865 | Exposure of prostate, any approach, for insertion of radioactive substance; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes |
| 81210 | BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg colon cancer) gene analysis, V600E variant |
| 81235 | EGFR (epidermal growth factor receptor) (eg non-small lung cancer) gene analysis, common variants (exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q) |
| 81504 | Oncology (tissue of origin), microarray gene expression profiling of > 2,000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reporting a risk score |
| 83950 | Oncoprotein; HER-2/neu |

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| 84233 | Receptor assay; estrogen |
| 84234 | Receptor assay; progesterone |
| 84999 | Unlisted chemistry procedure |
| 88239 | Tissue culture for neoplastic disorders; bone marrow, blood cells |
| 88240 | Cryopreservation, freezing and storage of cells, each cell line |
| 88241 | Thawing and expansion of frozen cells, each aliquot |
| 4179F | Tamoxifen or aromatase inhibitor |
| **HCPCS Level II Codes** | |
| S3854 | Gene expression profiling panel for the use in the management of breast cancer treatment |

Note: Inclusion on this list does not guarantee coverage

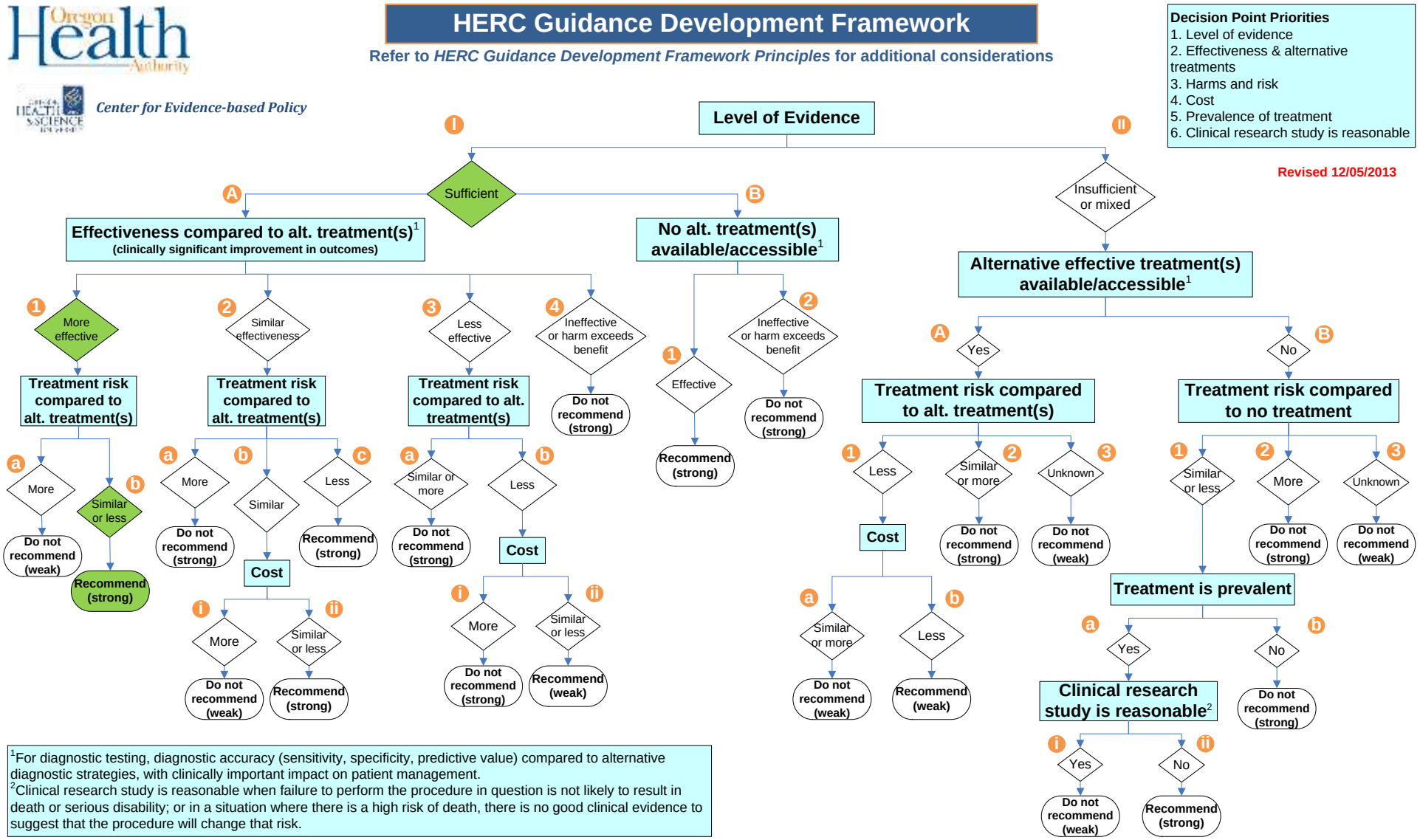
# APPENDIX C. HERC GUIDANCE DEVELOPMENT FRAMEWORK

HERC Guidance Development Framework Principles

This framework was developed to assist with the decision making process for the Oregon policy-making body, the HERC and its subcommittees. It is a general guide, and must be used in the context of clinical judgment. It is not possible to include all possible scenarios and factors that may influence a policy decision in a graphic format. While this framework provides a general structure, factors that may influence decisions that are not captured on the framework include but are not limited to the following:

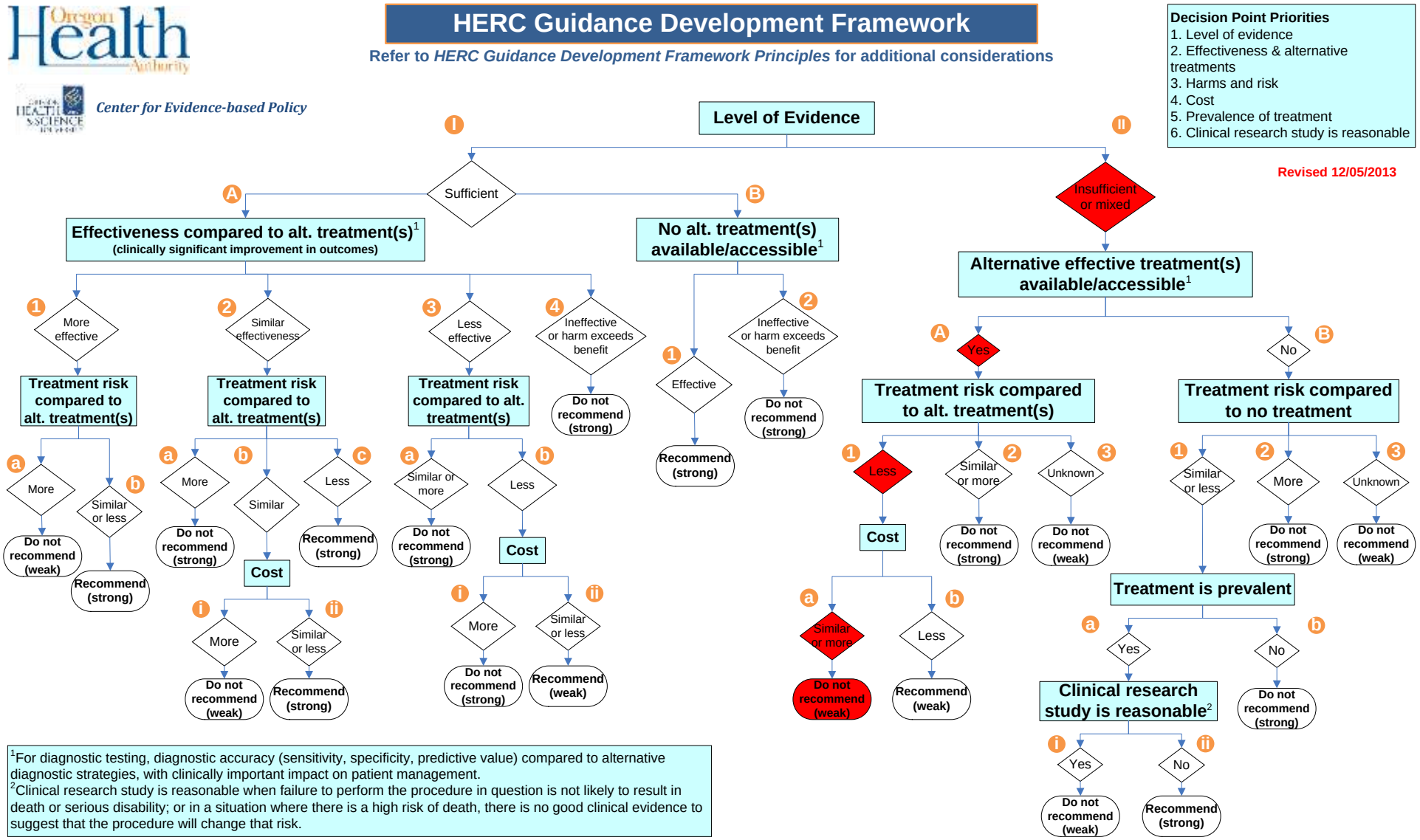
- Estimate of the level of risk associated with the treatment, or any alternatives;
- Which alternatives the treatment should most appropriately be compared to;
- Whether there is a discrete and clear diagnosis;
- The definition of clinical significance for a particular treatment, and the expected margin of benefit compared to alternatives;
- The relative balance of benefit compared to harm;
- The degree of benefit compared to cost; e.g., if the benefit is small and the cost is large, the committee may make a decision different than the algorithm suggests;
- Specific indications and contraindications that may determine appropriateness;
- Expected values and preferences of patients.

# Oncotype dx (lymph node negative breast cancer), BRAF (melanoma), KRAS (colorectal cancer), EGFR (lung 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.

# Oncotype dx (lymph node positive breast 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.

# Mammaprint (breast) IHC4 (breast), Mammostrat (breast), Prolaris/Oncotype DX (prostate), KRAS (lung), MIS (colorectal cancert), Oncotype dx (colorectal cancer), UroVysion (bladder)

Oregon Health Authority

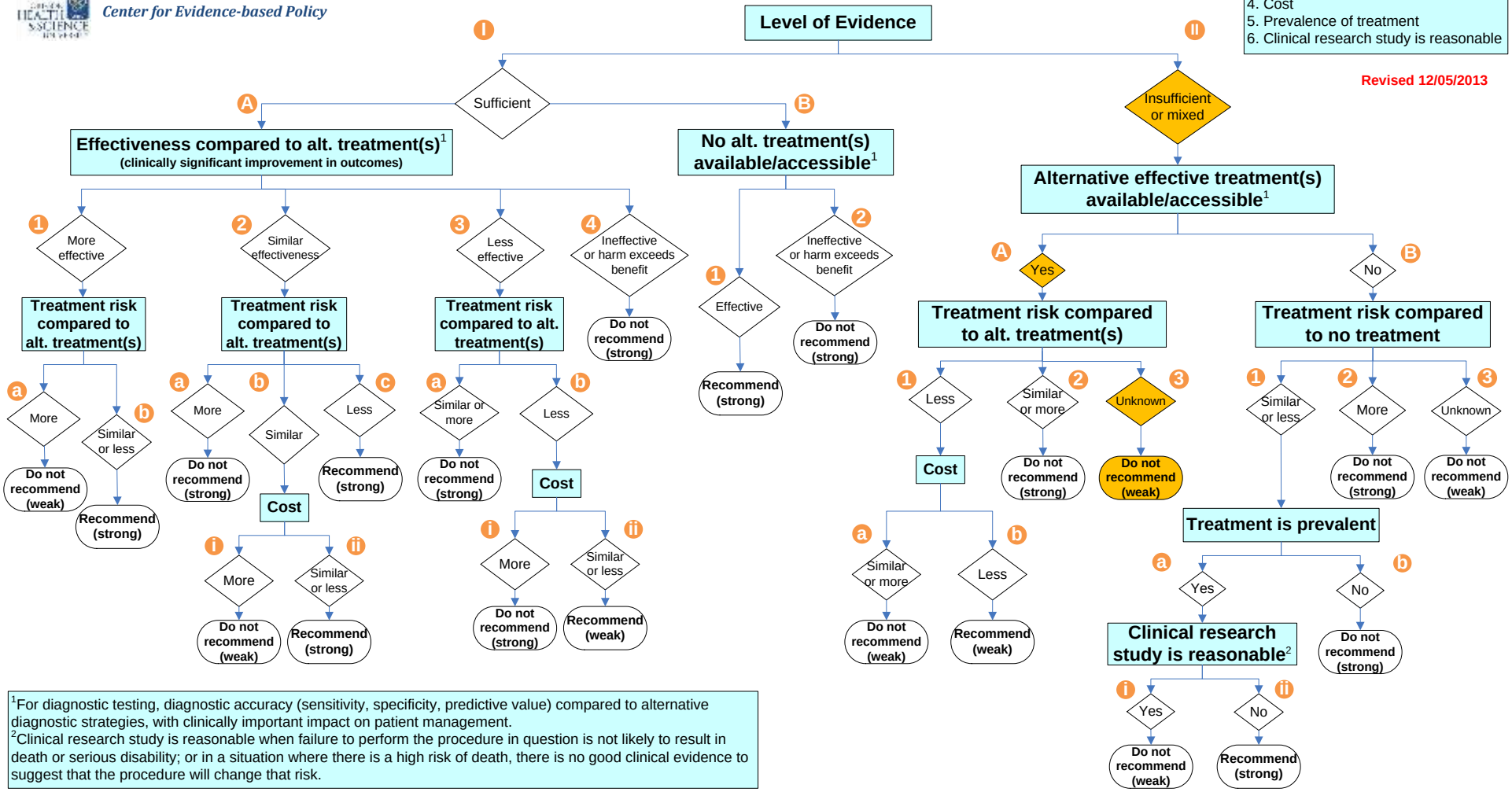
Center for Evidence-based Policy

## HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

**Decision Point Priorities**
1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Revised 12/05/2013




[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.

# BRAF (colorectal cancer)

Oregon Health Authority

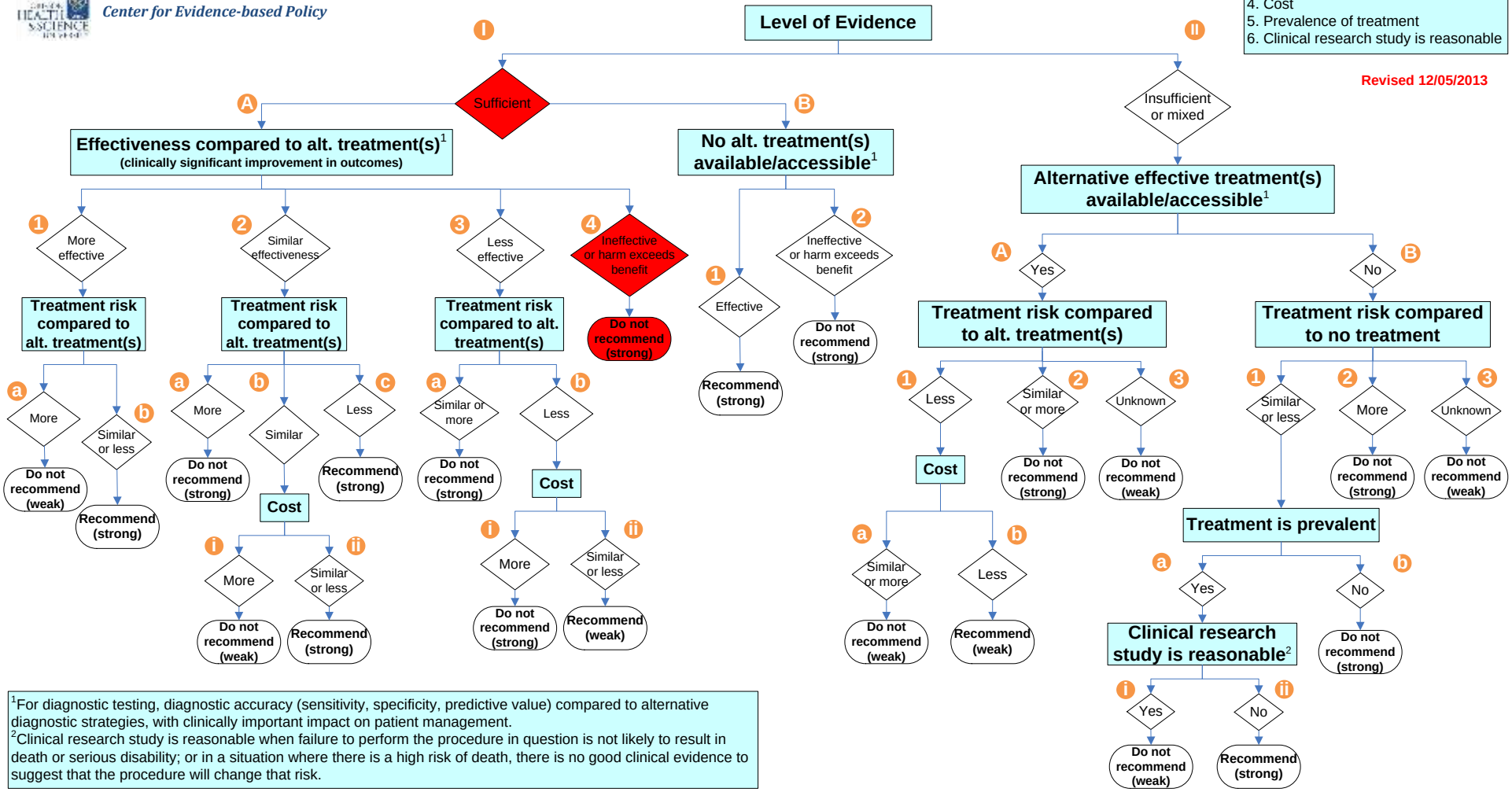
Center for Evidence-based Policy

## HERC Guidance Development Framework

Refer to *HERC Guidance Development Framework Principles* for additional considerations

**Decision Point Priorities**
1. Level of evidence
2. Effectiveness & alternative treatments
3. Harms and risk
4. Cost
5. Prevalence of treatment
6. Clinical research study is reasonable

Revised 12/05/2013




[1]For diagnostic testing, diagnostic accuracy (sensitivity, specificity, predictive value) compared to alternative diagnostic strategies, with clinically important impact on patient management.
[2]Clinical research study is reasonable when failure to perform the procedure in question is not likely to result in death or serious disability; or in a situation where there is a high risk of death, there is no good clinical evidence to suggest that the procedure will change that risk.