

Health Evidence Review Commission (HERC)

Coverage Guidance:

Genome Expression Profiling for Breast Cancer

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HERC Coverage Guidance

The following breast cancer genome profile tests (one test per primary breast cancer) are recommended for coverage in patients with early-stage breast cancer when the patient is willing to use the results of this testing in a shared-decision making process regarding adjuvant chemotherapy, and when the listed criteria are met:

- Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (*strong recommendation*). Lymph nodes with micrometastases less than 2 mm in size are considered node negative.
- EndoPredict (12 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (*weak recommendation*).
- Prosigna (50 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (*weak recommendation*).
- MammaPrint (70 gene) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk (*weak recommendation*).

Oncotype DX Breast Recurrence Score, EndoPredict, Prosigna, and MammaPrint are not recommended for coverage in early-stage breast cancer with involved axillary lymph nodes (*weak recommendation*).

Oncotype DX Breast DCIS Score is not recommended for coverage (*weak recommendation*).

Breast Cancer Index is not recommended for coverage (*weak recommendation*).

Note: Definitions for strength of recommendations are in Appendix A. *GRADE Informed Framework Element Description*.

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Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patient experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on clinical interventions and modes of care, evidence is evaluated using an adaptation of the GRADE methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness may be dependent on the environment in which the intervention is implemented.

GRADE-Informed Framework

HERC develops recommendations by using the concepts of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and makes an assessment of each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. The level of confidence in the estimate is determined by HERC based on the assessment of two independent reviewers from the Center for Evidence-based Policy.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, estimated resource allocation, values and preferences, and other considerations are assessments of HERC.

Should genome expression profiling be recommended for coverage for early-stage breast cancer?

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource Allocation	Values and Preferences	Other Considerations
Breast cancer mortality (Critical outcome)	Use of the 70-gene signature (MammaPrint) to determine recommendations for the use of adjuvant chemotherapy when there is a discordance between clinical and genomic risk classification does not result in statistically significant differences in the likelihood of five-year distant metastasis-free survival. ●●●○ (Moderate confidence, based on 1 RCT) In the per-protocol analysis of the same trial (which excluded patients who were ineligible, had a change in risk status, or did not adhere to the treatment assignment), patients with high clinical risk and low genomic risk who were treated based on their clinical risk (i.e., received adjuvant chemotherapy) had a higher rate of disease-free survival (93.3% vs. 90.3%, HR 0.63, 95% CI 0.43 to 0.95, p=0.03), but survival without distant metastasis and overall survival did not significantly differ. ●●○○ (Low confidence, based on per-protocol analysis of 1 RCT)	Coverage of genome expression profile testing would add significant cost, given the prevalence of breast cancer in the U.S. population and the price range of these tests. In cases that can be newly classified or convincingly confirmed as low risk based on these tests, there will be offsetting savings in chemotherapy avoided. Potentially, there could also be treatment savings in cases deemed as high risk by genome expression profiling, if earlier interventions result in more effective initial treatment.	Most women with early-stage breast cancer would highly value the additional information on treatment options informed by genome expression profile testing. Many (but not all) women classified as low risk would value the reassurance that chemotherapy would provide little or no benefit, and that the risks and side effects of treatment can be safely avoided. Similarly, women whose testing confirms high-risk status would value the knowledge that chemotherapy is	
Breast cancer morbidity (Critical outcome)	See above (the reported five-year distant metastasis-free survival and disease-free survival outcomes encompass morbidity as well as mortality).			

Should genome expression profiling be recommended for coverage for early-stage breast cancer?

Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource Allocation	Values and Preferences	Other Considerations
Change in management (Important outcome)	Use of genome expression profile tests (Oncotype DX Breast Recurrence Score, MammaPrint, EndoPredict, Prosigna) results in changes to treatments recommended or received (mainly for lymph node-negative patients) and contributes to the identification of patients who are likely or unlikely to benefit from adjuvant systemic chemotherapy. ●●●○ (Moderate confidence, based on 56 observational studies and 1 RCT)		necessary and likely beneficial. The value attributed to test results would be more variable in women who are clinically high risk, but for whom testing indicates low-risk status, and even less relied upon by women with lymph node involvement who are deemed low risk by genomic profiling.	
Quality of Life (Important outcome)	Insufficient data			
Harms (Important outcome)	Insufficient data			

Balance of benefits and harms: The clinical utility evidence base available to determine the balance of population benefits and harms is mainly limited to observational studies, but use of genome expression profile tests appears to consistently result in management decision changes that allow avoidance of adjuvant chemotherapy when scores indicating low risk are identified. Retrospective analysis of a prospective randomized adjuvant chemotherapy trial has validated the use of Oncotype DX Breast Recurrence Score in predicting chemotherapy benefit among women with estrogen receptor-positive, lymph node-negative breast cancer. One RCT utilizing MammaPrint demonstrated no significant difference in five-year metastasis-free survival and overall survival in the high clinical risk group. No safety concerns or direct harms are associated with use of these genomic tests.

Should genome expression profiling be recommended for coverage for early-stage breast cancer?

Outcomes	Estimate of Effect for Outcome/ <i>Confidence in Estimate</i>	Resource Allocation	Values and Preferences	Other Considerations
Rationale: We have moderate confidence that genome expression profile testing on patients with early-stage breast cancer results in changes to treatment recommendations and can help identify low-risk patient groups that are unlikely to benefit from adjuvant chemotherapy. Values and preferences weigh in favor of additional testing, which provides reassurance that the risks, side effects, and cost of chemotherapy can be safely avoided. There is insufficient evidence to support coverage of genome expression profile testing in early-stage breast cancer with positive lymph nodes, and values and preferences for reliance on such testing will be more variable among patients with lymph node involvement. Evidence of clinical utility is insufficient at present (small, single studies) to recommend coverage of Oncotype DX Breast DCIS Score to determine the use of radiotherapy following surgery for ductal carcinoma in situ, and insufficient to recommend coverage of Breast Cancer Index to predict the likelihood of benefit from extended (greater than five years) endocrine therapy. The recommendation for coverage of Oncotype DX Breast Recurrence Score is strong because the ability of that profile test to predict adjuvant chemotherapy benefit has the largest and best-established evidence base. The other coverage recommendations are weak because additional studies may better establish clinical utility and predictive value.				

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Outcomes	Estimate of Effect for Outcome/ Confidence in Estimate	Resource Allocation	Values and Preferences	Other Considerations
Recommendation: The following breast cancer genome profile tests (one test per primary breast cancer) are recommended for coverage in patients with early-stage breast cancer when the patient is willing to use the results of this testing in a shared-decision making process regarding adjuvant chemotherapy, and when the listed criteria are met: • Oncotype DX Breast Recurrence Score (21 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (<i>strong recommendation</i>). Lymph nodes with micrometastases less than 2 mm in size are considered node negative. • EndoPredict (12 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (<i>weak recommendation</i>). • Prosigna (50 gene) for breast tumors that are estrogen receptor positive, HER2 negative, and lymph node negative (<i>weak recommendation</i>). • MammaPrint (70 gene) for breast tumors that are estrogen receptor or progesterone receptor positive, HER2 negative, lymph node negative, and only in those cases categorized as high clinical risk (<i>weak recommendation</i>). Oncotype DX Breast Recurrence Score, EndoPredict, Prosigna, and MammaPrint are not recommended for coverage in early-stage breast cancer with involved axillary lymph nodes (<i>weak recommendation</i>). Oncotype DX Breast DCIS Score is not recommended for coverage (<i>weak recommendation</i>). Breast Cancer Index is not recommended for coverage (<i>weak recommendation</i>).				

Note: GRADE-informed framework elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Background

Approximately 1 in 8 women (12%) in the United States develop invasive breast cancer during their lifetime, making breast cancer the second most common cancer (following skin cancer) in American women (American Cancer Society [ACS], 2017). In 2014, there were 236,968 breast cancer diagnoses and 41,211 breast cancer deaths in women in the United States. In men, breast cancer is relatively rare, accounting for an additional 2,141 breast cancer diagnoses and 465 breast cancer deaths in 2014 (Centers for Disease Control and Prevention [CDC], 2017a).

Treatments for breast cancer include surgery, chemotherapy, hormonal therapy, biological therapy using the immune system, and radiation therapy (CDC 2017b). Genome expression profiling tests can be used to predict a cancer's aggressiveness, and thereby inform decision making on treatments. These tests analyze a sample of a cancer tissue to assess the activity level of certain genes, which may indicate the likelihood of the cancer growing and spreading. Other methods to predict cancer prognosis and aid in decision-making include web-based tools such as [Adjuvant! Online](#) and [PREDICT](#). Using patient and tumor characteristics (e.g., tumor size and grade, number of positive axillary nodes, hormone receptor status), these tools estimate the risk of cancer-related mortality or relapse without systemic adjuvant therapy, and then estimate the reduction of these risks if various therapy options are implemented.

Indications

The breast cancer genome expression profile tests Oncotype DX Breast Recurrence Score, EndoPredict, MammaPrint, Prosigna, and Breast Cancer Index (BCI) are indicated for women with early-stage, invasive breast cancer. Each of these tests can be used for estrogen receptor-positive (ER-positive) or hormone receptor-positive cancers. MammaPrint can also be used with ER-negative cancers. Oncotype DX and EndoPredict can only be used with cancers that are negative for human epidermal growth factor receptor 2 (HER2). The Oncotype DX Breast DCIS Score is indicated for women diagnosed with ductal carcinoma in situ. More detailed descriptions of the indications are provide in the technology description below.

Technology Description

The Oncotype DX Breast Recurrence Score test is used to predict the likely benefit of chemotherapy and the risk of distant recurrence among patients newly diagnosed with early-stage ER-positive, HER2-negative invasive breast cancer, both lymph node negative and lymph node positive. The Oncotype DX breast cancer assay uses reverse transcription polymerase chain reaction (RT-PCR) to measure the expression of 21 genes, including 16 cancer-related genes and five reference genes. The Oncotype DX Breast Recurrence Score ranges from zero to 100: higher numbers indicate a higher risk for distant recurrence and higher likelihood of chemotherapy benefit for that patient. The Oncotype DX report also provides a quantitative ER score by RT-PCR to help assess the magnitude of hormonal therapy benefit (Genomic Health, 2017a).

The Oncotype DX Breast DCIS Score is an assessment of 12 cancer-related genes that is performed on a tumor sample (after a biopsy or surgery) from a woman with DCIS. The Oncotype DX Breast DCIS Score results predict the 10-year risk of any local recurrence (DCIS or invasive carcinoma) or an invasive local recurrence, establish a baseline for consideration of the absolute risk reduction from radiation therapy, and provide quantitative ER and progesterone receptor (PR) single gene expression values (Genomic Health, 2017b).

The EndoPredict test is used to estimate the 10-year risk of distant recurrence of early-stage ER-positive, HER2-negative invasive breast cancer, both lymph node negative and lymph node positive. The EPclin risk score algorithm integrates a 12-gene molecular score, tumor size, and nodal status. The 12-gene molecular score uses quantitative RT-PCR on eight signature genes, three normalization genes, and one control gene. The EPclin score ranges from 1.0 to 6.0, and the test report includes the likelihood of distant metastasis if the patient receives five years of endocrine therapy alone (Myriad Genetic Laboratories, 2017).

The MammaPrint breast cancer recurrence assay is used to assess the likelihood of breast cancer recurrence among women with Stage I or Stage II invasive breast cancer, with a tumor size ≤ 5.0 cm, that is lymph node negative, ER positive or negative, and HER2 negative or positive. The assay assesses 70 genes using formalin-fixed paraffin-embedded tissue or fresh tissue for microarray analysis. MammaPrint uses an algorithm to classify patients as being at high or low risk of breast cancer recurrence (Agendia, 2017).

The Prosigna breast cancer gene signature assay is based on the PAM50 gene signature, which measures the expression of 50 genes to classify tumors into four intrinsic subtypes: luminal A, luminal B, HER2-negative enriched, and basal-like. Prosigna is indicated for use in postmenopausal women with hormone receptor-positive, lymph node-negative or lymph node-positive, Stages I, II, or IIIA breast cancer to be treated with adjuvant endocrine therapy. The Prosigna algorithm uses the PAM50 gene signature, intrinsic subtype, tumor size, nodal status, and proliferation score. The risk of recurrence score (ROR) is on a zero to 100 scale, which correlates with the probability of distant recurrence in a 10-year period (NanoString Technologies, 2017).

BCI predicts the likelihood of benefit from extended endocrine therapy among women with ER-positive, lymph node-negative or lymph node-positive (with one to three positive nodes), early-stage, invasive breast cancer. BCI provides an assessment of the likelihood of both late (post-five years) and overall (zero to 10 years) distant recurrence after an initial five years of endocrine therapy in lymph node-negative patients or five years of endocrine therapy plus adjuvant chemotherapy in lymph node-positive patients. BCI also predicts the likelihood of benefit from extended (>5 years) endocrine therapy (Biotheranostics, 2017).

Evidence Review

Systematic Reviews

Scope et al., 2017

This is a good-quality narrative systematic review of the use of genome expression profiling (GEP) and immunohistochemical (IHC) tests in adjuvant chemotherapy decisions for patients with breast cancer. The review was undertaken to inform the United Kingdom's National Institute for Health and Care Excellence (NICE) and was funded by the National Institute for Health Research. The authors reported no conflicts of interest. It includes 41 studies regarding MammaPrint, Oncotype DX, Mammostrat, and IHC4 testing published between 2002 and May 2016.

All of the included studies were observational, although five studies were based on a prospective analysis using archived tissue specimens from a larger adjuvant chemotherapy randomized controlled trial (RCT). These five studies were judged to be at moderate risk of bias. The remaining studies described changes in treatment recommendations or decisions based on GEP or IHC results and were

mainly limited by their small size, retrospective designs and incomplete reporting of patient characteristics. The authors also noted high levels of clinical heterogeneity among the studies.

Three of the included studies examined the ability of Oncotype DX breast cancer assay to predict adjuvant chemotherapy benefit among women with ER-positive, lymph node-negative breast cancer. The studies were based on archived tissue specimens from RCTs that compared endocrine therapy to endocrine therapy plus chemotherapy. In these studies, a high-risk 21-gene recurrence score was correlated with chemotherapy benefit defined by 10-year distant recurrence-free survival or disease-free survival. One of the three studies suggested that high-risk recurrence scores predicted benefit for chemotherapy among lymph node-positive patients and might be useful for avoiding adjuvant chemotherapy for patients with low recurrence score and positive nodes. The fourth study concluded that recurrence score offered the best predictive information about adjuvant chemotherapy benefit in ER-positive, lymph node-negative breast cancer. The authors noted that three of the four studies included data derived from National Surgical Adjuvant Breast and Bowel Project (NSABP) cohorts, which raises the possibility of double-counting in the systematic review.

The authors identified 28 studies of the effect of Oncotype DX on clinical decisions. These studies reported changes in adjuvant chemotherapy recommendations or receipt in 21% to 74% of the patients who were tested. All but one of the studies found overall decreases in the recommendation for or receipt of adjuvant chemotherapy; decreases ranged from 6% to 51%. The authors noted that in many studies it was not possible to determine whether the findings reported changes to the actual treatments received.

The authors identified six studies of how MammaPrint influenced clinical decisions. These studies reported overall changes in adjuvant chemotherapy recommendations or receipt in 18% to 40% of the patients who were tested. The studies found that overall, 2% to 32% of patients would have recommendations changed from adjuvant chemotherapy to no chemotherapy. The authors again noted difficulty in ascertaining the effects of the testing on actual treatments rendered. Two additional studies based on a prospective observational cohort in the Netherlands found that the use of MammaPrint would have increased recommendations for adjuvant chemotherapy from 48% (based on the Dutch Institute for Health Care Improvement guideline alone) to 62%, though MammaPrint would have lowered the rate of adjuvant chemotherapy recommendations compared to recommendations based on other guidelines (St Gallen, Nottingham Prognostic Index, and Adjuvant! Online). In the five-year follow-up study, 15% of low-risk patients by MammaPrint had received chemotherapy and the overall distant recurrence-free survival was 97%; among high-risk patients by MammaPrint, 81% received chemotherapy with a distant recurrence-free survival rate of 91.7%.

Overall, the authors concluded that Oncotype DX was “furthest along the validation pathway” and has “a reasonably large evidence base” with “some methodological weaknesses” (Scope et al., 2017, p. 42). The authors stated that new studies showed “MammaPrint is a strong independent prognostic factor” (Scope et al., 2017, p. 43), but noted that the populations in these studies were small. They also observed that the limited evidence and clinical heterogeneity made comparisons between tests difficult.

Harris et al., 2016

This is a clinical practice guideline from the American Society of Clinical Oncology on the use of biomarkers for adjuvant systemic chemotherapy decisions in women with early-stage breast cancer. The recommendations are apparently based on a systematic review of the clinical utility literature for these

tests, but the evidence findings are not described in sufficient detail to allow inclusion as part of this evidence review. The recommendations resulting from this review are discussed in the guideline section below.

Randomized Trials

Cardoso et al., 2016 (MINDACT)

This is a fair-quality prospective RCT of the clinical utility of the 70-gene signature (MammaPrint) test for early-stage breast cancer, as part of the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) study. Between 2007 and 2011, 6,693 patients were enrolled at 112 centers in nine European countries. Patients were eligible for enrollment if they were between the ages of 18 and 70 years old and had early-stage breast cancer (defined as T1 or T2 disease, or operable T3 disease). The study initially only enrolled patients without nodal involvement, but a protocol amendment in 2009 allowed patients with one to three positive axillary lymph nodes to enroll. Unlike most other studies of genome expression tests, patients with hormone receptor-negative and/or HER2-positive disease were included.

All patients were classified as clinically low risk or high risk using the Adjuvant! Online tool. Patients were considered clinically high risk if their 10-year probability of breast cancer-specific survival without adjuvant chemotherapy was less than 88% for ER-positive patients and 92% for ER-negative patients. All patients had genome expression testing on frozen tumor tissue using the 70-gene signature (70-GS) assay to classify them as genomically low or high risk. Patients with low clinical and genomic risk were advised against receiving adjuvant chemotherapy; patients with high clinical and genomic risk were advised to receive adjuvant chemotherapy. Patients with discordance between their clinical and genomic risk classification were randomized to adjuvant chemotherapy or no adjuvant chemotherapy. Randomization was stratified by institution, hormone receptor status, HER2 status, age, nodal status, and type of initial surgical resection. Patients were followed for a median of five years.

Overall, 41% of patients were classified as low clinical and genomic risk and 27% of patients were classified as high clinical and genomic risk. There were 690 patients with low clinical risk and high genomic risk (592 patients after correction, 8.8%). There were 1,497 patients classified as high clinical risk and low genomic risk (1,550 after correction, 23.2%). Within each of the discordant groups, patients were randomly assigned (1:1) to receive adjuvant treatment recommendations on the basis of their clinical or genomic risk classification. Overall adherence to the adjuvant chemotherapy recommendation was 86%.

In the intention-to-treat analysis, patients with high clinical and low genomic risk who were randomized to treatment based on their clinical risk assessment (i.e., recommended to receive chemotherapy) had a rate of distant metastasis-free survival of 95.9% at five years, compared to 94.4% among those randomized to treatment on the basis of their genomic risk assessment (i.e., recommended not to receive chemotherapy) (Hazard Ratio [HR] 0.78, 95% confidence interval [CI] 0.50 to 1.21). On the basis of these results, the authors observed that the use of the 70-GS would have led to an overall reduction in adjuvant chemotherapy in 46.2% of patients with high clinical risk. It should be noted that in the per-protocol analysis, five year disease-free survival was higher in the group treated with chemotherapy based on high clinical risk (93.3%) compared to those treated without chemotherapy based on low genomic risk (90.3%) (HR 0.64, 95% CI 0.43 to 0.95). Five-year overall survival and survival without distant metastases did not differ significantly between the treated arms in the per-protocol analysis. In a

subgroup analysis based on nodal status among patients with high clinical risk and low genomic risk, five-year survival without distant metastases was 95.7% and 93.2% for lymph node-negative patients randomized to chemotherapy or no chemotherapy respectively, and 96.3% and 95.6% for lymph node-positive patients randomized to chemotherapy or no chemotherapy respectively. It should be noted that lymph node-positive patients represented only about 20% of the overall study population.

In the intention-to-treat analysis of the group with low clinical risk and high genomic risk, patients randomized to chemotherapy on the basis of their high genomic risk had a rate of distant metastasis-free survival of 95.8% at five years compared to 95.0% for those randomized to no chemotherapy on the basis of their low clinical risk (HR 1.17, 95% CI 0.59 to 2.28). Thus, in the population of patients with low clinical risk, there is no advantage to offering chemotherapy to patients with high genomic risk. Similarly, five-year survival without distant metastases, disease-free survival, and overall survival did not vary based on the treatment received in the per-protocol analysis for this group, although there was greater imprecision in the estimates of effect.

Potential sources of bias in this trial include the use of multiple regimens among those randomized to systemic chemotherapy and the use of different hormonal therapies among women with ER-positive disease. There was also a protocol revision in 2010 to address a misclassification of high genomic risk in 162 patients stemming from a change in the RNA-extraction solution. An additional 113 patients had their clinical or genomic risk reclassified after enrollment. The study was funded by several research foundations, some of which accept donations from industry. Additional data are being collected to determine outcomes beyond five years.

The findings of this study suggest that patients deemed to be at high clinical risk may avoid the use of adjuvant chemotherapy when they are classified as low genomic risk by the 70-GS without a statistically significant increase in distant metastasis or death at five years of follow-up.

Ongoing Trials

In addition to the longer-term outcomes of the MINDACT study, the randomized portion of two studies (TAILORx and RxPONDER) involving the Oncotype DX 21-RS score and a UK National Health Service study comparing genome expression test-guided treatments for early-stage breast cancer (OPTIMA) are ongoing.

Additional Observational Studies

Additional observational studies published after the dates of the search conducted by Scope and colleagues (2017) are briefly summarized in Table 1.

Table 1: Additional Recent Observational Trials

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Sanft et al., 2015 Breast Cancer Index Funding source not disclosed Three authors reported conflicts of interest related to employment, shareholding, or honoraria from the maker of BCI	Prospective case series with decision impact analysis Single center Connecticut 2014	N = 153 ER-positive, Stage I-III breast cancer patients receiving adjuvant endocrine therapy for at least 3.5 years	Pre- and post-BCI treatment recommendations were available for 96 patients. Before BCI results, 49% were assessed as low risk for recurrence after 5 years (defined as <5% risk), 38% were assessed as intermediate risk (6% to 15% risk of recurrence after 5 years), and 13% were assessed as high risk (>15% risk of recurrence after 5 years). Overall, before BCI results, extended endocrine therapy was recommended for 71 women (74%); after BCI results, treatment recommendations changed for 25 patients and extended endocrine therapy was recommended for 52 patients (54%); most of the changes in treatment recommendation occurred in patients classified as low risk by BCI; 29% fewer patients reported that they planned to pursue extended endocrine therapy after testing. BCI was also associated with more accurate risk perception, reduced decisional conflict, and reduced anxiety.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Ettl et al., 2017 EndoPredict (11-gene expression assay) and Protein marker uPA/PAI-1 No specific funding reported Two authors reported past employment, patents, or honoraria from the maker of EndoPredict	Prospective consecutive case series comparing treatment decisions with and without information from EndoPredict EPclin and/or protein marker uPA/PAI-1 (a protein marker test commonly used in Germany) Single center Germany 2012-2015	N = 395 Invasive, intermediate risk, ER-positive, HER2-negative breast cancer (Intermediate risk as classified by the Interdisciplinary S3-Guideline)	EPclin results were obtained for all 395 patients, among whom 250 patients were classified as low risk and 145 as high risk. uPA/PAI-1 results were obtained for 190 patients, among whom 46% were classified as low risk and 54% as high risk. Overall, the tests showed concordant risk stratification in 59% of patients. In the analysis of all patients, the results of EPclin (with uPA/PAI-1 results when available) did not affect treatment recommendation in 225 patients (57%), led to a recommendation of adjuvant chemotherapy in 20 patients (5%), and led to a recommendation against adjuvant chemotherapy in 150 patients (38%). Among the patients with results for both EPclin and uPA/PAI-1, when assessed independently, EPclin results led to changes in treatment recommendation in 87 patients (46%); uPA/PAI-1 led to changes in treatment recommendations in 46 patients (24%).

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Kuijter et al., 2017 MammaPrint (70-gene expression assay) Funded by Agendia NV One of the authors reported conflicts of interest	Prospective case series with decision impact analysis Multi-center Netherlands 2013-2015	N = 698 patients with early-stage, ER-positive, HER2-negative, pN0-N1 breast cancer	Pre-GEP treatment decisions were for adjuvant chemotherapy in 41% of patients and against adjuvant chemotherapy in 16% of patients; in the remaining cases, clinicians preferred to wait for the GEP before making a recommendation. Among patients for whom a pre-GEP treatment recommendation was rendered, that recommendation changed after the GEP results in 51% of patients. Overall, the rate of actual adherence to the treatment recommendation was 91% and was similar whether the recommendation was for or against adjuvant chemotherapy.
Kuijter et al., 2016(a) MammaPrint (70-gene expression assay) Funded by the Dutch Cancer Society Authors reported no conflicts of interest	Cross-sectional study using the Netherlands Cancer Registry Population-based Netherlands 2011-2013	N = 2,043 women under age 70 with ER-positive, HER2-negative, pN0-pN1mi, grade I-II invasive breast cancer	Overall, 298 eligible patients (15%) received 70-GS testing; 70-GS testing was more likely in younger women with smaller tumors and more limited axillary lymph node involvement. After adjustment for measured confounders, the 70-GS was associated with 9.5% reduction in the absolute risk of receiving adjuvant chemotherapy in the linear mixed-effects model; the observed reduction in the rate of chemotherapy use was statistically significant only among women under age 50.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Pohl et al., 2016 MammaPrint (70-gene expression assay) Funded by the South African Medical Research Council One author reported a conflict of interest	Retrospective case series with decision impact analysis Multi-center South Africa 2007-2014	N = 107 patients with hormone receptor-positive, HER2-negative, 0-3 positive nodes, invasive breast cancer and available 70-gene expression assay results	Overall, 60 patients were considered clinically high risk and 47 were clinically low risk; 56 patients had treatment changes based on 70-GS results. Among clinically high-risk patients, 37 (62%) with low-risk 70-GS results did not receive chemotherapy. Among clinically low-risk patients, 19 (40%) with high-risk 70-GS results received chemotherapy
Tsai et al., 2017 MammaPrint (70-gene expression assay) Funded by Agendia Eight authors reported various conflicts of interest	Prospective case series with decision impact analysis Multi-center United States 2012-2015	N = 840 patients with ER-positive, HER2-negative, 0-3 positive nodes and an intermediate risk (RS 18-30) by 21-gene expression assay testing	Overall, the initial treatment recommendations (after 21-gene assay but before 70-GS) were for adjuvant chemotherapy in 45.5% of patients; recommendations for adjuvant chemotherapy were more likely as the recurrence score increased. Among 374 patients with a low-risk 70-GS, 108 (28.9%) had chemotherapy omitted from their treatment recommendation; among the 466 patients with a high-risk 70-GS 171 (36.7%) had chemotherapy added to their treatment recommendation.
Kuijjer et al., 2016(b) MammaPrint (70-gene expression assay) or Oncotype DX Breast Recurrence score (21-gene expression assay) Funded by the Dutch Cancer Society Conflicts of interest were not reported	Retrospective historically controlled cohort Population-based Netherlands 2004-2006 2012-2014	N = 3,864 women with ER-positive, HER2-negative, pN0-N1mi, grade I-II invasive breast cancer	A guideline change between the historical and contemporary cohorts resulted in an overall increase in the use of adjuvant chemotherapy (9% to 40%), but use of GEP was associated with a smaller and nonsignificant increase in the use of chemotherapy between the two cohorts (21% to 28%, $p = 0.191$). Adherence to the treatment recommendations based on GEP results were similar for the 70-GS (91%) and the 21-RS (89%) in the contemporary cohort.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Bear et al., 2017 Oncotype DX Breast Recurrence Score (21-gene expression assay) on core needle biopsy specimen Funded by Genomic Health Inc. and an NCI grant One author reported speaking advisory board honoraria from Genomic Health Inc.	RCT of neoadjuvant hormonal treatment vs. neoadjuvant systemic chemotherapy among patients with recurrence score (RS) 11-25 Multi-center United States and Canada	N = 64 cN0, cN1a or CN2a; hormone receptor positive, HER2 negative, with tumors >2cm desiring breast-conserving surgery Patients with RS <11 received neoadjuvant hormonal therapy (NHT) Patients with RS 11-25 were randomized to NHT or neoadjuvant chemotherapy (NCT) Patients with RS >25 received NCT	Among 55 patients with complete follow-up, the overall distribution of recurrence scores was: - RS <11 = 12 - RS 11-25 = 29 - RS >25 = 14 In the RS 11-25 group, 18 patients received NHT and 11 patients received NCT (some patients assigned to NCT refused treatment and 2 crossed to the NHT group) In as-treated analysis, patients with RS 11-25 who received NCT were more likely to have a clinical response (72.7% vs. 50%, $p = 0.049$), but there was no statistically significant difference in the rate of successful breast-conserving surgery (63.6% vs. 72.2%, $p = \text{NS}$), which was the primary outcome for the study.
Barcenas et al., 2017 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funded by an NCI grant One author reported serving on a scientific advisory board for MammaPrint	Retrospective descriptive analysis Single center Texas 2005-2011	N = 1,424 Stage I-II, hormone receptor-positive HER2 negative, lymph node negative	Rate of adjuvant chemotherapy by risk score: - RS <11 = 1.7% - RS 11-25 = 15% - RS >25 = 73.4% Among those with RS 11-25, overall invasive disease-free survival at 5 years was 92.6% (95% CI 89.6 to 94.7) and there were no statistically significant differences between those who received adjuvant chemotherapy and those who did not with respect to invasive disease-free survival (HR 1.64, 95% CI 0.73 to 3.71), relapse-free survival (HR 1.46, 95% CI 0.41 to 5.23), or overall survival (HR 2.19 95% CI 0.44 to 11).

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Dzimitrowicz et al., 2017 Oncotype DX Breast Recurrence Score (21- gene expression assay) Funding not reported Seven authors reported various potential financial conflicts	Retrospective historically controlled cohort investigating early ordering of RS (before or at the time of surgery rather than the time of the postoperative visit) Single center Connecticut July-December 2015 (Historical controls January-June 2015)	N = 90 in the early RS testing group (N = 76 in the historical control group) Patients under age 80 years with invasive breast cancer, tumor size >0.5 cm to <5 cm ER positive, HER2 negative, lymph node negative (clinically or pathologically)	In the early RS group, 82 of 90 eligible patients had an RS ordered (91%) compared to 58 of 76 patients (76%) in the control group. Overall, 21% of patients received adjuvant chemotherapy. Median time to chemotherapy decision was 20 days in the early RS group compared to 32 days in the control group ($p < 0.001$), but there were no differences between the groups in rate of chemotherapy use, time to chemotherapy start, or the average costs of testing plus planned treatment. Most (80%) of the medical oncologists surveyed reported that the early RS results were useful.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Friese et al., 2017 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funding by NCI, CDC, and the California Department of Public Health One author reported research funding from multiple sources including Genomic Health Inc. and Myriad Genetics Laboratories Inc.	Cross-sectional survey using SEER and Genomic Health Inc. registries Population-based study in Los Angeles County and Georgia 2013-2014	N = 1,527 Early-stage breast cancer survey respondents	Overall, 60% of the sample had received RS testing; the rate of RS testing varied by risk group: 62.6% for lymph node negative with favorable disease, 24.3% for lymph node negative with less favorable disease, and 13% for lymph node-positive disease. There were no statistically significant differences in the likelihood of RS testing based on educational attainment, income, or race; women with 2 or more comorbidities were less likely to receive RS testing than those with no comorbidities (OR 0.5, 95% CI 0.3 to 0.7). Compared with no RS testing, RS testing was associated with a lower likelihood of receiving adjuvant chemotherapy in the low RS group (OR 0.1, 95% CI 0.1 to 0.2) and a higher likelihood of receiving adjuvant chemotherapy in the intermediate RS (OR 1.4, 95% CI 1.1 to 1.7) and high RS (OR 2.8, 95% CI 2.8 to 4) groups. Patients reported high levels of satisfaction with RS testing and 64% rated it as very or extremely helpful in their decision making.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Gluz et al., 2016 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funding support from Genomic Health Inc., Sanofi Aventis, and Amgen Inc. Ten of the authors reported varied conflicts of interest including honoraria, consulting, employment, or ownership	Prospective cohort derived from a larger RCT of adjuvant chemotherapy; trial was amended to recommend endocrine therapy only in patients with RS <11 Multi-center Germany 2009-2011	N = 2,274 Mainly pN0-N1 (94%) Hormone receptor positive, HER2 negative	Overall, 404 patients had RS <11 with 86% adherence to the recommendation for endocrine therapy only; 1,397 patients had RS 12-25 with 78.6% adherence to recommendation for chemotherapy; 473 patients had RS >25 with 89.7% adherence to recommendation for chemotherapy. In the analysis of treatment adherers, 3-year disease-free survival was 98.4% in the RS <11 group, 97.5% in the RS 12-25 group, and 94.9% in the RS >25 group. In a multivariate analysis of predictors of disease-free survival, RS, nodal status, and tumor grade were independent prognostic factors.
Jasem et al., 2017 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funding source not reported Authors reported no conflicts of interest	Retrospective cohort using the National Cancer Database Population-based study in the US 2010-2012	N = 10,434 patients with pT1-T2, pN1 (1-3 nodes involved), hormone receptor-positive, HER2-negative breast cancer who had a known RS assay ordered compared to 21,991 women with similar disease profile and no RS score	After adjustment for other factors that predict likelihood of adjuvant chemotherapy, patients exposed to RS testing were less likely to receive chemotherapy than those who did not receive RS testing (aOR 0.21, 95% CI 0.20 to 0.22); compared to a low-risk RS (<18) referent, intermediate (18-30) and high-risk (>30) RS were associated with a greater likelihood of receiving adjuvant chemotherapy (aOR of 4.5 and 20, respectively). RS testing was less likely to be performed in Black patients, those treated at community medical centers, uninsured or governmentally insured patients, and those with poorer prognostic features; Black patients who were tested were more likely to have high-risk RS scores.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Kozick et al., 2017 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funding source not reported Authors reported no conflicts of interest	Cross-sectional study using the National Cancer Database Population-based study in the US 2010-2012	N = 158,235 women with ER-positive, HER2-negative, lymph node-negative breast cancer, tumor size >0.5 cm, who had received partial or total mastectomy and who had no evidence of metastatic disease	Overall, 56,323 patients (35.6%) received RS testing. Factors that predicted greater odds of RS testing were younger age, white race/ethnicity, residence in a higher income area, treatment at an academic medical center, and private insurance. Larger tumor size, total mastectomy, and higher comorbidity score were associated with lower odds of RS testing. Among 30,011 patients classified as low risk by RS score, 95% adhered to the guideline-based recommendation to omit adjuvant chemotherapy. Among 4,278 patients classified as high risk, 89.6% adhered to the guideline-based recommendation to receive adjuvant chemotherapy. 44% of patients in the intermediate-risk group received adjuvant chemotherapy; younger age, larger tumor size, and higher RS score were associated with greater odds of receiving chemotherapy in this group.
Leung et al., 2016 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funded by Genomic Health Inc. Two authors reported conflicts of interest related to employment	Prospective case series with impact decision analysis Six centers Hong Kong	N = 146 patients with early-stage breast cancer, ER positive, HER2 negative, pN0-pN1mi	Overall, 34 (23.3%) pre-RS-score treatment recommendations changed after the RS-score was made available to clinicians; in 28 cases there was a decrease in recommended treatment intensity, and in 7 cases there was an increase in recommended treatment intensity.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Pestalozzi et al., 2017 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funded in part by the Swiss State Secretariat for Education, Research, and Innovation One author reported lecture fees from Genomic Health Inc.	Prospective case series with decision impact analysis Multicenter Switzerland 2013-2014	N = 222 patients with ER-positive, HER2-negative, pN0-pN1a	Overall, 154 patients were considered low risk and 68 were considered non-low risk prior to RS score results. In the low-risk group, RS score led to changes in treatment recommendations for 23 patients (15%); recommendations for 5 patients changed to include chemotherapy and recommendations for 18 patients changed to omit chemotherapy. In the non-low risk group, RS score led to changes in treatment recommendations for 22 patients (32%); recommendations for 3 patients changed to include chemotherapy while recommendations for 19 patients changed to omit chemotherapy.
Stemmer et al., 2017 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funded by Teva Pharmaceuticals Nine authors reported various conflicts of interest	Retrospective registry analysis Single center Israel 2006-2010	N = 1,801 patient with ER-positive, HER2-negative, lymph node-negative invasive breast cancer	Overall, 880 patients (48.9%) had RS <18, 733 patients (40.7%) had RS 18-30, and 188 (10.4%) had RS >30. 1.4% of patients with RS <18, 23.7% of patients with RS 18-30, and 87.2% of patients with RS >30 received adjuvant chemotherapy. At median follow-up of 6.2 years, distant recurrence was observed in 0.8% of patients with RS <18, 3.0% of patients with RS 18-30, and 8.6% of patients with RS >30; within the intermediate risk group, there was no difference in the 5-year distant recurrence risk or time to distant recurrence between the adjuvant chemotherapy and untreated groups.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Loncaster et al., 2017 Oncotype DX Breast Recurrence Score (21-gene expression assay) Funded in part by Genomic Health Inc. Three authors reported conflicts of interest	Prospective case series with decision impact analysis Multi-center Manchester, England 2012-2015	N = 210 patients with ER-positive, HER2-negative, intermediate clinical risk invasive breast cancer (Note: 1/3 of women were postmenopausal and node positive)	All patients had an initial recommendation for adjuvant chemotherapy; after RS results, 37% underwent chemotherapy and 63% received endocrine therapy only. Among patients with a low-risk RS (<18), 4.7% of patients received chemotherapy; 54% of patients with intermediate-risk RS (18-30) received chemotherapy with a greater likelihood among those with a higher RS; 85% of patients with RS >30 received chemotherapy. A budget impact analysis based on this study suggested that the avoidance of chemotherapy afforded by use of the GEP made the test cost saving (under an assumption that all patients initially recommended for chemotherapy would receive it).
Manders et al., 2016 Oncotype DX DCIS (12-gene expression assay for DCIS) Funded by Genomic Health Inc. Twelve of the authors reported conflicts of interest	Prospective case series with a decision impact analysis Thirteen sites United States 2014-2015	N = 127 patients with histologically confirmed pure DCIS who were candidates for breast-conserving surgery and were radiotherapy naive	Before the DCIS score results, 72% of recommendations were to receive radiotherapy. Most patients (66%) had low DCIS scores, 20% had intermediate scores, and 14% had high scores. Overall, 26.4% of treatment recommendations changed after the DCIS score; 15% of recommendations changed from radiotherapy to no radiotherapy and 11.4% were from no radiotherapy to radiotherapy; surgeons were more likely than radiation oncologists to recommend against radiotherapy in the low DCIS score group . Among a small number of patients with completed questionnaires, use of the DCIS score was associated with reduced decisional conflict and anxiety.

Study: Gene expression assay(s) Funding and conflicts	Design Setting	Population	Results
Hequet et al., 2017 Prosigna (50-gene expression assay) Funded by NanoString Technologies Inc. Four of the authors reported employment conflicts of interest	Prospective consecutive case series with decision impact analysis Multi-center France 2015-2016	N = 210 Postmenopausal women with Stage I-II, ER-positive, HER2-negative, lymph node-negative breast cancer	Compared to pre-GEP treatment recommendations, knowledge of the genome expression assay results led to change in adjuvant treatment recommendation in 34 patients (18%); 25 patients changed from a recommendation of no adjuvant to chemotherapy to a recommendation for chemotherapy, and 9 recommendations for adjuvant chemotherapy were changed to no chemotherapy. 75% of physicians agreed or strongly agreed that the GEP provided valuable information. There were statistically significant differences in patient-reported anxiety, decisional conflict, and emotional wellbeing (Note: There was significant loss to follow-up for collection of patient-reported outcomes measures).
Wuerstlein et al., 2016 Prosigna (50-gene expression assay) Funded by NanoString Technologies Inc. Seven authors reported various conflicts of interest	Prospective consecutive case series with decision impact analysis 11 centers Germany 2013-2014	N = 198 postmenopausal women with ER-positive, HER2-negative, lymph node-negative early-stage breast cancer	Prior to GEP results, adjuvant chemotherapy was recommended for 45 patients (22.7%). Overall, 50-gene expression assay results led to a change in recommendation about adjuvant chemotherapy in 27 cases; this was mainly due to a greater number of recommendations for adjuvant chemotherapy (20) among patients with high- or intermediate-risk 50-gene expression assay scores.

Clinical Validity

The following section was added at the request of the subcommittee to address questions about whether the tests had equivalent clinical validity and to provide more in depth information on the Albain study of patients with lymph node positive disease.

Blok et al., 2017

A recent systematic review by Blok et al. (2018) summarized the available clinical validity studies of breast cancer genome expression tests. The authors identified 50 clinical validation studies including 21 studies of MammaPrint, 20 studies of Oncotype DX, five studies of Prosigna, and four studies of EndoPredict. The authors cautioned that differences in the patient populations and clinical outcome measures across the studies made it difficult to compare the tests. Meta-analysis was not performed, but the authors observed that the tests were generally able to distinguish between high and low genomic risk and that those classifications were correlated with various prognostic measures (e.g., distant metastasis-free survival, recurrence-free survival, loco-regional recurrence). Table 2 summarizes the range of reported hazard ratios for outcomes incorporating survival in genomically low-risk patients compared to genomically high risk patients. Using the framework proposed by Simon et al. (2009) (excerpted as Figure 1), the authors concluded that Prosigna and EndoPredict have Level B evidence of clinical validity, and Oncotype DX and MammaPrint each have at least one Level A trial.

Table 2. Hazard ratios for outcomes incorporating survival in genomically low-risk patients compared to genomically high-risk patients

Test	Range of reported hazard ratios comparing genomically low-risk to genomically high-risk patients (higher hazard ratios indicate better prognostic performance)
MammaPrint	Distant metastasis-free survival: 2.7 to 5.7 Overall survival: 2.2 to 10.7
Oncotype DX	Distant recurrence-free survival: 2.12 to 6.09
Prosigna	Recurrence-free survival: 1.98
EndoPredict	Local recurrence-free survival: 1.31

Table 1. Elements of tumor marker studies that constitute Levels of Evidence determination*

Category Element	A Prospective	B Prospective using archived samples	C Prospective/observational	D Retrospective/observational
Clinical trial	PCT designed to address tumor marker	Prospective trial not designed to address tumor marker, but design accommodates tumor marker utility Accommodation of predictive marker requires PRCT	Prospective observational registry, treatment and follow-up not dictated	No prospective aspect to study
Patients and patient data	Prospectively enrolled, treated, and followed in PCT	Prospectively enrolled, treated, and followed in clinical trial and, especially if a predictive utility is considered, a PRCT addressing the treatment of interest	Prospectively enrolled in registry, but treatment and follow-up standard of care	No prospective stipulation of treatment or follow-up; patient data collected by retrospective chart review
Specimen collection, processing, and archival	Specimens collected, processed, and assayed for specific marker in real time	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion	Specimens collected, processed, and archived prospectively using generic SOPs. Assayed after trial completion	Specimens collected, processed and archived with no prospective SOPs
Statistical design and analysis	Study powered to address tumor marker question	Study powered to address therapeutic question and underpowered to address tumor marker question Focused analysis plan for marker question developed before doing assays	Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study Focused analysis plan for marker question developed before doing assays	Study not prospectively powered at all. Retrospective study design confounded by selection of specimens for study No focused analysis plan for marker question developed before doing assays
Validation	Result unlikely to be play of chance Although preferred, validation not required	Result more likely to be play of chance than A but less likely than C Requires one or more validation studies	Result very likely to be play of chance Requires subsequent validation studies	Result very likely to be play of chance Requires subsequent validation

* PCT = prospective controlled trial; PRCT = prospective randomized controlled trial; SOPs = standard operating practices.

Figure 1. Excerpted from Simon et al., 2009

The review also summarized studies of clinical utility, including one study each of EndoPredict and Prosigna. The included clinical utility study of EndoPredict (Muller et al., 2013) examined treatment decisions among 167 women with T1-3, N1-3, HER2-negative, HR-positive breast cancer. Before testing, adjuvant chemotherapy was recommended for 63.8% of patients, which decreased to 47.7% after testing. The included clinical utility study of Prosigna (Martin et al., 2015) examined treatment decisions among 200 women with T1-2, N0, HER2-negative, HR-positive breast cancer. Before testing, adjuvant chemotherapy was recommended for 30% of patients, which decreased to 28% after testing.

Buus et al., 2016

An additional clinical validity study published after the search dates of the Blok et al. systematic review compared the clinical validity of the EndoPredict EP or EpiClin scores to Oncotype DX RS using the same archived specimens from the ATAC trial (Buus et al., 2016). The ATAC trial was a randomized controlled trial comparing anastrozole, tamoxifen, or a combination of the two medications for adjuvant treatment of postmenopausal women with ER-positive, HER2-negative localized breast cancer. In the trial,

approximately 60% of women were lymph node-negative, 25% had one to three positive lymph nodes, and 10% had more than four positive lymph nodes. The various genomic scores were assessed from 928 specimens from the original trial (680 specimens were from lymph node-negative patients and 248 were from lymph node-positive patients). In the first five years, EP and RS performed similarly in predicting distant recurrence-free survival ($LR\chi^2$ 25.7 vs. 26.1, respectively). EPclin (which incorporates clinical features into the algorithm) showed the greatest association with distant recurrence-free survival ($LR\chi^2$ 80.0) among tests incorporating genomic information. In years 5 to 10, EPclin had the best correlation with distant recurrence-free survival among the genomic tests ($LR\chi^2$ 59.3 vs. 23.6 for EP and 5.6 for RS). However, in both time frames, the clinical treatment score (CTS, a score calculated from information on nodal status, tumor size, tumor grade, and age that was derived from the ATAC dataset) offered the greatest prognostic value ($LR\chi^2$ 85.0 in years 0 to 5 and 64.7 in years 5 to 10). An analysis combining the genomic tests with CTS vs. CTS alone showed that each test offered incremental prognostic information over CTS alone, and EPclin + CTS showed the best prognostic performance in years 5 to 10.

Sestak et al, 2017

An additional clinical validity study published after the search dates of the Blok et al. systematic review compared the clinical validity of the EpiClin score, Oncotype DX RS, Prosigna ROR, BCI, CTS, and the four-marker immunohistochemical score (IHC) using the archived specimens from the ATAC trial. The ATAC trial is described above. For this analysis, the various genomic scores were calculated from 774 specimens (591 from patients with lymph node-negative disease and 183 from patients with lymph node-positive disease). In the univariate analysis for predicting distant recurrence at zero to 10 years, all the studied indices offered prognostic information but showed greater prognostic discernment in lymph node-negative patients (see Table 3).

Table 3. Hazard ratios for distant recurrence

	HR for distant recurrence (0-10 years) in LN- patients (95% CI)	HR for distant recurrence (0-10 years) in LN+ patients (95% CI)
CTS	1.99 (1.58 to 2.50)	1.63 (1.20 to 2.21)
IHC4	1.95 (1.55 to 2.45)	1.33 (0.99 to 1.78)
RS	1.69 (1.40 to 2.03)	1.39 (1.05 to 1.85)
BCI	2.46 (1.88 to 3.23)	1.67 (1.21 to 2.29)
ROR	2.56 (1.96 to 3.35)	1.58 (1.16 to 2.15)
EPclin	2.14 (1.71 to 2.68)	1.69 (1.29 to 2.22)

Overall, the authors concluded that all of the studied indices offered prognostic information for distant recurrence in postmenopausal women with ER-positive, HER2-negative localized breast cancer, but that the prognostic value is attenuated in LN-positive patients. However, scores that incorporate clinical and genomic variables tended to perform better in LN-positive patients. The study was independently funded, but seven of the authors disclosed various conflicts of interest with the manufacturers of the genomic tests.

Albain et al., 2010

This study was a prospective-retrospective validation of the Oncotype DX RS in patients with node-positive breast cancer. The study used 367 archived specimens from the SWOG 8814 trial, which compared tamoxifen alone to six cycles of adjuvant chemotherapy (cyclophosphamide, doxorubicin, and 5-fluorouracil [CAF]), followed by tamoxifen (CAF-T). Specimens from a third arm of the parent trial, which used concurrent tamoxifen and CAF, were excluded from analysis since this treatment was inferior to CAF-T. Compared to the overall population from the parent trial, patients whose specimens were included in this analysis had slightly fewer positive nodes and smaller tumors.

The authors found that the RS was prognostic for disease-free survival (DFS) among patients in the tamoxifen-only arm of the trial; for low-risk RS, the 10-year DFS was 60% compared to 49% in the intermediate-risk group and 43% in the high-risk group. The rates of 10-year overall survival were 77%, 68%, and 51% in the low-, intermediate-, and high-risk groups respectively. However, the authors observed that the hazard ratios were not constant over time and that for patients who survived beyond five years, the RS was no longer prognostic.

The RS was also predictive of whether patients would benefit from CAF-T. For patients with low-risk RS (< 18), the HR for 10-year DFS with CAF-T compared to tamoxifen alone was 1.02 (95% CI 0.54 to 1.93) and for 10-year overall survival was 1.18 (95% CI 0.55 to 2.54). For patients with intermediate-risk RS (18 to 30), the HR for 10-year DFS with CAF-T compared to tamoxifen alone was 0.72 (95% CI 0.39 to 1.31) and for 10-year overall survival was 0.84 (95% CI 0.40 to 1.78). For patients with high-risk RS (> 31), the HR for 10-year DFS with CAF-T compared to tamoxifen alone was 0.59 (95% CI 0.35 to 1.01) and for 10-year overall survival was 0.56 (95% CI 0.31 to 1.02). The authors observed that the interaction between RS and adjuvant chemotherapy benefit was significant after adjustment for age, race, tumor size, tumor grade, progesterone receptor status, and p53 and HER2 status. However, adjusting for ER level (which contributes to the RS) rendered the interaction non-significant.

Evidence Summary

A growing number of observational clinical utility studies have found that genome expression testing for patients with early-stage breast cancer results in changes to adjuvant treatment recommendations and can help identify low-risk patient groups that are unlikely to benefit from adjuvant chemotherapy. There is no evidence that directly compares different genome expression profiling tests with respect to clinical utility. Although there is a growing body of evidence for the use of these tests in lymph node-positive patients, there is still uncertainty about the effects of these tests on treatment decisions and clinical outcomes in this population, and an evidence-based clinical practice guideline from the American Society of Clinical Oncology in 2016 recommends against their use in lymph node-positive patients.

There are only small, single studies regarding the clinical utility of gene expression profiling for neoadjuvant treatment decisions or for determining the use of radiotherapy after surgery for ductal carcinoma in situ, and these studies have not reported on long-term clinical outcomes.

On the basis of a single RCT, patients (including those with one to three positive nodes, representing about 20% of the overall study population) who were considered high risk by clinical classification but low risk by genomic classification utilizing MammaPrint can forgo adjuvant chemotherapy without a statistically significant reduction in the likelihood of distant metastasis-free survival at five year follow-up. Additional RCTs are underway.

Policy Landscape

Payer Coverage Policies

Medicaid

The Washington Medicaid [Physician-Related Services/Health Care Professional Services Billing Guide \(11/12/2017\)](#) specifies coverage for Oncotype DX breast cancer assay and EndoPredict, but does not mention Oncotype DX DCIS, MammaPrint, Prosigna, or BCI. Oncotype DX for breast cancer and EndoPredict are covered when these conditions are met:

- Test is performed within six months of the diagnosis
- Node negative (micrometastases less than 2mm in size are considered node negative)
- Hormone receptor positive
- Tumor size 0.6 to 1.0 cm with moderate/poor differentiation or unfavorable features (i.e., angiolymphatic invasion, high nuclear grade, high histologic grade) OR tumor size >1 cm
- Unilateral disease
- HER2 negative
- Patient will be treated with adjuvant endocrine therapy
- The test result will help the patient make decisions about chemotherapy when chemotherapy is a therapeutic option

Medicare

No National Coverage Determinations were found for the Oncotype DX breast cancer assay, Oncotype DX DCIS, EndoPredict, MammaPrint, Prosigna, or BCI. Local Coverage Determinations (LCDs) were found for Oncotype DX DCIS, EndoPredict, Prosigna, and BCI. No LCDs were found for the Oncotype DX Breast Recurrence Score, or MammaPrint.

Five LCDs were found for [Oncotype DX DCIS](#). The LCDs provide coverage for Oncotype DX DCIS when these conditions are met:

- Pathology (excisional or core biopsy) reveals ductal carcinoma in situ of the breast (no pathological evidence of invasive disease)
- FFPE specimen with at least 0.5 mm of DCIS length
- Patient is a candidate for and is considering breast-conserving surgery alone as well as breast-conserving surgery combined with adjuvant radiation therapy
- Test result will be used to determine treatment choice between surgery alone vs. surgery with radiation therapy
- Patient has not received and is not planning on receiving a mastectomy

One LCD was identified for [EndoPredict](#). This LCD provides coverage for EndoPredict when these conditions are met:

- T1-3, N0-1 breast cancer
- Patient is postmenopausal
- Pathology reveals invasive carcinoma of the breast that is ER positive, HER2 negative
- Patient is either node negative or has one to three positive lymph nodes
- Patient has no evidence of distant metastasis

- Test result will be used to determine treatment choice between endocrine therapy alone vs. endocrine therapy plus chemotherapy

Five LCDs were identified for [Prosigna](#). These LCDs provide coverage for Prosigna for postmenopausal women who have either ER-positive, node-negative, Stage I or Stage II breast cancer, or ER-positive, node-positive (one to three positive nodes), Stage II breast cancer.

Five LCDs were identified for [BCI](#), which provide coverage when these criteria are met:

- Postmenopausal female with non-relapsed, ER-positive breast cancer
- Node negative
- Patient is completing five years of tamoxifen therapy
- Patient is eligible for consideration of extended endocrine therapy based on published clinical trial data or practice guidelines
- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects
- The test results will be discussed with the patient, including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current cancer management guidelines

Private Payers

The policies for Aetna, Cigna, Moda, and Regence were reviewed for coverage of the Oncotype DX breast cancer assay, Oncotype DX DCIS, EndoPredict, MammaPrint, Prosigna, and BCI.

The [Aetna policy](#) (last reviewed 11/7/2017) provides coverage for the Oncotype DX breast cancer assay, EndoPredict, MammaPrint, Prosigna, and BCI under specified criteria. Aetna does not cover Oncotype DX DCIS.

The following are the criteria for Aetna's coverage for each of the tests, the Oncotype DX breast cancer assay, EndoPredict, MammaPrint, Prosigna, and BCI, to assess the necessity of adjuvant chemotherapy in females or males with recently diagnosed breast tumors:

- Adjuvant chemotherapy is not precluded by any other factor (e.g., advanced age or significant comorbidities)
- Prior to testing, the patient and physician have discussed the potential results of the test and agree to use the results to guide therapy (i.e., member will forgo adjuvant chemotherapy if Oncotype DX score is low)

The following are Aetna's additional criteria for the Oncotype DX breast cancer assay:

- Breast cancer is nonmetastatic (node negative) or with one to three involved ipsilateral axillary lymph nodes
- Breast tumor is ER positive
- Breast tumor is HER2 negative or breast tumor is HER2 positive and less than 1 cm in diameter

The following are Aetna's additional criteria for MammaPrint:

- Breast cancer is nonmetastatic (node negative) or with one to three involved ipsilateral axillary lymph nodes
- Breast tumor is ER positive or PR positive
- Breast tumor is HER2 negative

- Member is determined to be at "high clinical risk" of recurrence using Adjuvant! Online (www.adjuvantonline.com)

The following are Aetna's additional criteria for EndoPredict, Prosigna Breast Cancer Prognostic Gene Signature Assay, and BCI:

- Breast cancer is nonmetastatic (node negative)
- Breast tumor is ER positive
- Breast tumor is HER2 negative

The [Regence policy](#) (last reviewed August 2017) provides coverage for the Oncotype DX breast cancer assay, EndoPredict, and BCI under certain conditions. Regence does not cover Oncotype DX DCIS, MammaPrint or Prosigna.

Regence covers the Oncotype DX breast cancer assay, EndoPredict, and BCI for women with primary breast cancer, Stages I, II, or III, to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy when these criteria are met:

- Individual has had excision of breast mass and full pathologic evaluation of the specimen has been completed (i.e., the test should not be ordered on a preliminary core biopsy)
- Primary tumor size 0.6 cm to 1 cm with moderate/poor differentiation or unfavorable features, OR tumor size of 1 cm or greater
- If there are multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing
- Hormone receptor positive
- HER2 negative
- Negative lymph nodes (nodes with micrometastases of 2 mm or less in size are considered node negative)
- The test result will aid the patient in making a decision regarding chemotherapy when chemotherapy is a therapeutic option

The [Cigna policy](#) (effective date 11/15/2017) covers the Oncotype DX breast cancer assay, MammaPrint, and Prosigna under certain conditions, and does not provide coverage for Oncotype DX DCIS, EndoPredict, or BCI.

The following are Cigna's coverage criteria for the Oncotype DX breast cancer assay:

- Recently diagnosed Stage I or Stage II breast cancer
- ER positive
- HER2 negative
- No evidence of distant metastasis
- Either of the following criteria:
 - Axillary-node status is negative (micrometastasis is no greater than 2.0 mm) whether the woman is pre- or postmenopausal
 - Up to three positive axillary nodes in a postmenopausal woman

The following are Cigna's coverage criteria for MammaPrint:

- Stage I or Stage II invasive breast cancer
- High clinical risk of recurrence

- ER positive/progesterone receptor positive
- HER2 negative
- Up to three positive nodes

The following are Cigna's coverage criteria for Prosigna:

- Recently diagnosed Stage I or Stage II breast cancer
- ER positive
- HER2 negative
- Postmenopausal
- No evidence of distant metastasis
- Axillary node status is negative (micrometastasis is no greater than 2.0 mm)

The [Moda policy](#) (last reviewed 10/25/2017) provides coverage for the Oncotype DX breast cancer assay with [prior authorization](#). No coverage policy was identified for Oncotype DX DCIS, EndoPredict, MammaPrint, BCI, or Prosigna.

Recommendations from Others

Three guidelines were identified on the use of genome expression profiling for breast cancer:

- *Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women with Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline* (Harris et al., 2016)
- *Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women with Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update* (Krop et al., 2017)
- *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer* (National Comprehensive Cancer Network [NCCN], 2017)
- *Gene Expression Profiling and Expanded Immunohistochemistry Tests for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer Management: MammaPrint, Oncotype DX, IHC4 and Mammostrat* (National Institute for Health Care Excellence [NICE], 2013)

American Society of Clinical Oncology

The 2016 guidelines from the American Society of Clinical Oncology outlined recommendations for each of the genome expression profiling tests for women with early-stage invasive breast cancer and with known ER/PR and HER2 status, as outlined below.

Oncotype DX

- If a patient has ER/PR-positive, HER2-negative (node-negative) breast cancer, the clinician can use Oncotype DX to guide decisions on adjuvant systemic chemotherapy.
- If a patient has ER/PR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use Oncotype DX to guide decisions on adjuvant systemic chemotherapy.
- If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use Oncotype DX to guide decisions on adjuvant systemic therapy.

EndoPredict

- If a patient has ER/PR-positive, HER2-negative (node-negative) breast cancer, the clinician can use EndoPredict to guide decisions on adjuvant systemic chemotherapy.
- If a patient has ER/PR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use EndoPredict to guide decisions on adjuvant systemic chemotherapy.
- If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use EndoPredict to guide decisions on adjuvant systemic therapy.

Prosigna (PAM50 risk of recurrence score)

- If a patient has ER/PR-positive, HER2-negative (node-negative) breast cancer, the clinician can use the Prosigna score, in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy.
- If a patient has ER/PR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use Prosigna to guide decisions on adjuvant systemic therapy.
- If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use Prosigna to guide decisions on adjuvant systemic therapy.

Breast Cancer Index

- If a patient has ER/PR-positive, HER2-negative (node-negative) breast cancer, the clinician can use BCI to guide decisions on adjuvant systemic therapy.
- If a patient has ER/PR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use BCI to guide decisions on adjuvant systemic therapy.
- If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use BCI to guide decisions on adjuvant systemic therapy.

Mammostrat

If a patient has ER/PR-positive, HER2-negative (node-positive or node-negative) breast cancer, the clinician should not use the five-protein assay to guide decisions on adjuvant systemic therapy.

If a patient has HER2-positive breast cancer or triple-negative breast cancer, the clinician should not use the five-protein assay (Mammostrat) to guide decisions on adjuvant systemic therapy.

MammaPrint

The 2017 guideline update from the American Society of Clinical Oncology focused on modifying the recommendations regarding MammaPrint, based on recently published studies. The new recommendations for MammaPrint are below.

- If a patient has ER/PR-positive, HER2-negative, node-negative breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy because of its ability to identify a good-prognosis population with potentially limited chemotherapy benefit.
- If a patient has ER/PR-positive, HER2-negative, node-negative breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer.

- If a patient has ER/PR-positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay may be used in patients with one to three positive nodes and at high clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy because of its ability to identify a good-prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node.
- If a patient has ER/PR-positive, HER2-negative, node-positive, breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population.
- If a patient has HER2-positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy.
- If a patient has ER/PR-negative and HER2-negative (triple negative) breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy.

National Comprehensive Cancer Network

The NCCN guidelines included discussion of Oncotype DX (21-gene breast cancer assay), MammaPrint (70-gene assay), and Prosigna (50-gene assay). The Oncotype DX assay is to be considered with pT1, pT2, or pT3, and pN0 or pN1mi, and the tumor is greater than 0.5 cm. The guidelines concluded that the Oncotype DX assay was the best validated breast cancer assay.

National Institute for Health Care Excellence

The 2013 NICE guidelines recommended Oncotype DX as an option for guiding adjuvant chemotherapy decisions for people with ER-positive, node-negative, and HER2-negative early breast cancer when the patient is assessed as being at intermediate risk and the Oncotype DX results are likely to help in predicting the course of the disease, and therefore help when making the decision about prescribing chemotherapy. MammaPrint and Mammostrat are only recommended for use in research in patients with ER-positive, node-negative, and HER2-negative early breast cancer. The NICE guidelines did not address Oncotype DX DCIS, EndoPredict, Prosigna, and BCI.

Quality Measures

No quality measures related to genome expression profiling for breast cancer were identified when searching the [National Quality Measures Clearinghouse](#).

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Appendix A. GRADE-Informed Framework Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical

sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

DRAFT

Appendix B. GRADE Evidence Profile

Quality Assessment (Confidence in Estimate of Effect)							
No. of Studies	Study Design(s)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Factors	Quality
Breast cancer mortality							
1	RCT	Moderate	N/A	Not serious	Not serious		Moderate ●●●○
Breast cancer morbidity							
1	RCT	Moderate	N/A	Not serious	Not serious		Moderate ●●●○
Quality of Life							
							Insufficient evidence
Harms							
							Insufficient evidence
Change in management							
57	1 RCT, remainder observational studies of various types	Moderate	Not serious	Not serious	Not serious		Moderate ●●●○

Appendix C. Methods

Scope Statement

Populations

Women diagnosed with early-stage breast cancer

Population scoping notes: None

Interventions

Genome expression profiling on cancer tissue

Intervention exclusions: None

Comparators

Usual care, immunohistochemical assays, genome expression profiling tests compared to each other

Outcomes

Critical: Breast cancer morbidity, breast cancer mortality

Important: Quality of life, harms, change in management of breast cancer

Considered but not selected for the GRADE table: Analytic validity, clinical validity

Key Questions

KQ1: What is the comparative effectiveness of genome expression profiling in early-stage breast cancer?

KQ2: How does the comparative effectiveness of genome expression profiling vary by:

- a. Age
- b. Race or ethnicity
- c. Patient and family history
- d. Cancer characteristics (e.g., tumor size, tumor grade, type of tumor, nodal status, hormone receptor status, HER2 status, proliferation rate, cancer stage)
- e. Menopausal status

KQ3: What are the harms of genome expression profiling for breast cancer?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2012.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)
Blue Cross/Blue Shield Center for Clinical Effectiveness
Canadian Agency for Drugs and Technologies in Health (CADTH)
Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)

Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-Effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms breast cancer and Oncotype (21-gene) or Endopredict (12-gene) or Mammaprint (70-gene) or Mammostrat or Breast Cancer Index (PAM50) or Prosigna. The search was limited to publications in English published since 2012. In addition, a MEDLINE® search was conducted for randomized controlled trials published after the search dates of the most recent systematic review selected for each intervention.

Searches for clinical practice guidelines were limited to those published since 2012. A search for relevant clinical practice guidelines was conducted using MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Guidelines Clearinghouse
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English, did not address the scope statement, or were study designs other than systematic reviews, meta-analyses, technology assessments, clinical utility studies, or clinical practice guidelines.

Appendix D. Applicable Codes

CODES	DESCRIPTION	Assay
CPT Codes		
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score	Oncotype DX
81599	Unlisted multianalyte assay with algorithmic analysis	EndoPredict
88381	Microdissection (i.e., sample preparation of microscopically identified target); manual	
81479	Unlisted molecular pathology procedure	MammaPrint, Breast Cancer Index
84999	Unlisted chemistry procedure	MammaPrint
HCPCS codes		
S3854	Gene expression profiling panel for use in the management of breast cancer treatment	EndoPredict, MammaPrint
Multianalyte Assays with Algorithmic Analyses (MAAA) codes		
0008M	Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score	Prosigna

Note: Inclusion on this list does not guarantee coverage.