Protocol

Genetic Testing for Breast Cancer Gene Expression Prognosis Assay

(20436, 20476)

(Content formerly found in: Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients With Breast Cancer and Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers)

Medical Benefit		**Effective Date**: 07/01/17	**Next Review Date**: 09/17
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Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With early-stage node-negative invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling testing	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With early-stage node-positive invasive breast cancer considering adjuvant chemotherapy	Interventions of interest are: • Gene expression profiling testing	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With ductal carcinoma in situ considering radiotherapy	Interventions of interest are: • Gene expression profiling testing	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Change in disease status
Individuals: • With early-stage node-negative invasive breast cancer free of distant recurrence at 5 years	Interventions of interest are: • Gene expression profiling testing	Comparators of interest are: • Clinical risk prediction algorithms	Relevant outcomes include: • Disease-specific survival • Change in disease status
Individuals: • With breast cancer who are undergoing assessment of HER2 status	Interventions of interest are: • Assessment of HER2 status using quantitative total HER2 protein expression and HER2 homodimer measurement	Comparators of interest are: • Assessment of HER2 status using immunohistochemis-try or fluorescence in situ hybridization	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity

Description

Laboratory tests have been developed that detect the expression, via messenger RNA, of many different genes in breast tumor tissue and combine the results into a prediction of distant recurrence risk for women with early-stage breast cancer. Test results may help providers and patients decide whether to include adjuvant chemotherapy in postsurgical management of breast cancer or to alter treatment in patients with ductal carcinoma in situ (DCIS).

Novel assays that quantitatively measure total human epidermal growth factor receptor 2 (HER2) protein expression and homodimers have been developed to improve the accuracy and consistency of HER2 testing.

Summary of Evidence

For all tests and all indications, relevant outcomes include disease-specific survival and changes in disease status.

Early-Stage Node-Negative Invasive Breast Cancer

Only studies presenting ten year distant recurrence rates in node-negative women not receiving adjuvant chemotherapy were included in this review. In addition to negative nodes, the type of patient considered for this indication have positive hormone receptors and are human epidermal growth factor receptor 2 (HER2) negative.

21-Gene Assay (Oncotype DX)

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), the evidence includes multiple prospective clinical trials and prospective-retrospective studies. Patients classified as low risk with Oncotype DX have a low risk of recurrence in which avoidance of adjuvant chemotherapy is reasonable (average risk at 10 years, 7%-9%; upper bound of the 95% confidence intervals, 11% to 15%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

70-Gene Signature (MammaPrint)

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 70-gene signature (MammaPrint), the evidence includes one study with outcomes in node-negative patients. Although the study showed a low risk of 10-year distant recurrence, it did not derive from high-quality data sources. A recently reported study of clinical utility only reported five year results and may not identify a group with sufficiently low risk. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Prosigna, the evidence includes two prospective-retrospective studies evaluating the prognostic ability of Prosigna. Both studies showed a low absolute risk of distant recurrence in patients with low risk scores. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Early-Stage Node-Positive Invasive Breast Cancer

70-Gene Signature (MammaPrint)

For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy

who receive gene expression profiling with the 70-gene signature (MammaPrint), the evidence includes prospective-retrospective studies. Existing studies have not reported 10-year distant recurrence outcomes in the patients of interest. The studies are confounded by various factors (e.g., receipt of treatment) or do not report the outcome of interest. The evidence is insufficient to determine the effects of the technology on health outcomes.

Continuation of Tamoxifen Therapy Beyond Five Years

EndoPredict

For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at five years considering extending tamoxifen treatment who receive gene expression profiling with EndoPredict, the evidence includes one study of archived tissue samples from a previously conducted clinical trial. The study showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.

Breast Cancer Index

For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at five years considering extending tamoxifen treatment who receive gene expression profiling with BCI, the evidence includes two studies of archived tissue samples from previously conducted clinical trials. The study showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.

HER2

The evidence for assessment of HER2 status using quantitative total HER2 protein expression and HER2 homo-dimer measurement in patients who have breast cancer and are undergoing assessment of HER2 status includes validation studies and retrospective analysis of association between levels and survival outcomes. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Retrospective analysis using HERmark® have shown that the assay may predict a worse response to trastuzumab in certain populations. However, findings have been inconsistent, and no clear association with clinical outcomes has been shown. Additionally, cut points for defining patient groups varied across studies. Clinical utility of the HERmark® assay has not been demonstrated, and clinical trials are needed to determine the impact on clinical outcomes of patients stratified by the HERmark® assay. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

The use of gene expression assays for deciding the value of adjuvant therapy in individuals with intermediate risk breast cancer may be considered **medically necessary** for women with breast cancer meeting all of the following characteristics:

- Unilateral tumor; AND
- hormone receptor-positive (that is estrogen-receptor [ER]-positive or progesterone receptor [PR]-positive); AND
- human epidermal growth factor receptor 2 (HER2) negative; AND
- tumor size 0.6 to one cm with moderate/poor differentiation or unfavorable features OR tumor size larger than one cm; AND

- node negative or lymph nodes with micrometastases less than two mm in size; AND
- who will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors; AND
- when the test result will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option); AND
- when ordered within six months after diagnosis.

The use of the Oncotype DX or Prosigna RT-PCR assays may be considered **medically necessary** if the individual meets the criteria above.

Gene expression assays for deciding the value of adjuvant therapy in individuals with intermediate risk breast cancer and with ER+, Her2-cases with one to three ipsilateral lymph nodes may be considered **medically necessary**.

The 21-gene RT-PCR assay Oncotype DX™ should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should be ordered in the context of a physician-patient discussion regarding risk preferences and when the test result will aid the patient in making decisions regarding chemotherapy.

For patients who otherwise meet the above characteristics but who have multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

All other indications for multigene breast cancer panel assays, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes or patients with bilateral disease, are considered **investigational**.

The use of a subset of genes from the Oncotype DX or Prosigna RT-PCR assay for predicting recurrence risk in individuals with noninvasive ductal carcinoma in situ to inform treatment planning following excisional surgery is considered **investigational**.

The use of other gene expression assays, including but not limited to MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test, the Breast Cancer Index^{SM}, BreastOncPx^{TM}, NexCourse® Breast IHC4, BreastPRS™, and EndoPredict™ for any indication is considered **investigational**.

The use of gene expression assays in men with breast cancer is considered **investigational**.

The use of gene expression assays to molecularly subclassify breast cancer is considered **investigational**.

The use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression is considered **investigational**.

The use of gene expression assays in tumors that are hormone receptor positive, Her2 Negative, or less than or equal to .5 cm is **investigational**.

Medicare Advantage

The above medical necessity criteria applies for Medicare Advantage members for all gene expression assays in breast tumor tissue tests when no separate Medicare Advantage criteria exists.

The Prosigna breast cancer gene signature assay may be considered **medically necessary** for members that meet the following criteria consistent with the FDA indications for use:

- Post-menopausal female **either**

- ER+, lymph node-negative, stage I or II breast cancer; or
- ER+, lymph node-positive (1-3 positive nodes), stage II breast cancer.

PROSIGNA® Breast Cancer Prognostic Gene Signature Assay is considered **medically necessary** in patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care, either as:

- A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-negative, Stage I or II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors.
- A prognostic indicator for distant recurrence-free survival at 10 years in post-menopausal women with Hormone Receptor-Positive (HR+), lymph node-positive (one to three positive nodes), Stage II breast cancer to be treated with adjuvant endocrine therapy alone, when used in conjunction with other clinicopathological factors. The device is not intended for patients with four or more positive nodes.

The Breast Cancer Index (aka BCI) (bioTheranostics) may be considered **medically necessary** for members that meet the following criteria:

- Post-menopausal female with non-relapsed, ER+ BREAST CANCER, and
- Was lymph node negative, and
- Is completing five (5) years of tamoxifen therapy, and
- Patient must be eligible for consideration of extended endocrine therapy based on published clinical trial data or practice guidelines, and
- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects, and
- 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).

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 is considered **medically necessary** to guide therapeutic decision-making in patients with the following findings:

- estrogen-receptor positive, node-negative carcinoma of the breast
- estrogen-receptor positive micrometastases of carcinoma of the breast, and
- estrogen-receptor positive breast carcinoma with one to three positive nodes.

The Oncotype DX DCIS assay is **medically necessary** only when the following clinical conditions are met:

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

For Medicare Advantage the HERmark®, Oncotype DX® Breast and the MammaPrint™ tests may be considered **medically necessary**.

Background

An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant treatments. For example, for women with early-stage, invasive breast cancer (i.e., cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk of recurrence. Women with the best prognosis have small tumors, are estrogen receptor–positive, and are lymph node–negative. These women have an approximately 15% baseline risk of recurrence; approximately 85% of these patients would be disease-free at 10 years with tamoxifen treatment alone and could avoid the toxicity of chemotherapy, if they could be accurately identified. Conventional risk classifiers (e.g., Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. Consensus guidelines for defining receptor status exist.[1] However, no single classifier is considered a criterion standard, and several common criteria have qualitative or subjective components that add variability to risk estimates. As a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help women's decision making, some who may prefer to avoid chemotherapy if assured that their risk is low.

In other clinical scenarios involving breast cancer, accurate assessment of prognosis may affect the decision to offer certain treatments. Recently, several groups have identified panels of gene expression markers ("signatures") that appear to predict the baseline risk of invasive breast cancer recurrence after surgery, radiotherapy, and endocrine therapy (for hormone receptor–positive tumors). Several gene expression tests commercially available in the United States are listed in Table 1. If these panels are more accurate risk predictors than current conventional classifiers, they could be used to aid decision making on adjuvant treatments without greatly affecting disease-free survival and overall survival (OS). This review focuses on gene expression profiling (GEP) panels that have prognostic or predictive ability in individuals with early-stage, invasive breast cancer with known estrogen receptor and progesterone receptor and human epidermal growth factor receptor (HER2) status. The proposed clinical utility of these tests varies depending on the clinical context; these specific indications are discussed in this review:

1. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.
2. Prognosis and/or prediction of treatment response in patients with node-positive (one to three nodes), early-stage, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.
3. Prognosis and/or prediction of treatment response in patients with ductal carcinoma in situ (DCIS) for the purpose of determining whether patients can avoid radiation therapy.
4. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, HER2-negative invasive breast cancer, receiving adjuvant hormonal therapy, who have survived without progression to five years postdiagnosis, for the purpose of determining whether patients should continue adjuvant hormonal therapy.

For each of these clinical indications, clinical trials have shown that there is some clinical benefit to receiving the additional therapy under consideration. However, each of the additional treatments has potential adverse effects. If a patient subgroup can be defined that has an extremely low risk of distant recurrence, or a subgroup

can be defined that does not respond to the treatment, then the additional treatment can be forgone with little effect on cancer outcome due to the low risk of poor outcome or lack of response to treatment.

Table 2. Gene Expression Tests Reporting Recurrence Risk for Breast Cancer Considered Herein

Test	Manufacturer	Description
Oncotype DX	Genomic Health (Redwood City, CA)	21-gene RT-PCR
EndoPredict	Sividon Diagnostics (acquired by Myriad [Salt Lake City, UT] in 2016)	12-gene real-time RT-PCR
Breast Cancer Index	bioTheranostics (San Diego, CA)	Combines MGI and the HOXB13:IL17BR Index using RT-PCR
MammaPrint	Agendia (Amsterdam, The Netherlands)	70-gene DNA microarray
Prosigna	NanoString Technologies (Seattle, WA)	nCounter® digital analysis system based on PAM50 breast cancer intrinsic subtype classifier

MGI: Molecular Grade Index; PAM50: prediction analysis of microarray 50 gene set; RT-PCR: reverse transcriptase polymerase chain reaction.

Additional commercially available tests may provide some prognostic or predictive information for breast cancer. Tests intended to assess estrogen receptor, progesterone receptor, and HER2 status, such as TargetPrint® (Agendia; via quantitative microarray), are outside the scope of this review. In addition, tests that do not provide a specific recurrence risk are outside the scope of this review.

Other commercially available biomarkers are designed to provide information about tumors' molecular subtypes (i.e., luminal A, luminal B, HER2 type, and basal type). Prosigna was initially offered as a molecular subtype test. The BluePrint 80-gene molecular subtyping assay (Agendia) is offered in combination with MammaPrint to augment predictive data about response to chemotherapy.

Many studies have investigated individual biomarkers or combinations of biomarkers that are associated with breast cancer outcomes. Determining which studies constitute sufficient evidence that the test or biomarker is likely to be clinically useful depends on attributes of the test such as its performance and the quality of the study generating the results. Simon et al has described a framework to evaluate prognostic biomarker evidence.[2] Study designs such as prospective clinical trials or previously conducted clinical trials with archived tumor samples constitute stronger evidence than studies with less planned and systematic patient recruitment and data collection. Randomized trials allow determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcome in the patient group of interest that would result in a change in management (e.g., withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show consistency of results and more than one study demonstrating the desired result should be available. Simon has proposed that at least two Simon category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker.[2]

The main outcome of interest to this review is 10-year distant recurrence-free survival. Distant recurrence is a hallmark of advanced breast cancer and thus more informative of OS than disease-free survival. Disease-free survival also includes local recurrence, which has a much better treatment prognosis than distant disease. For one of the indications in this review, the main outcome of interest is 10-year distant recurrence-free survival conditional on recurrence-free survival for five years. There is no definitive threshold for an acceptable trade-off of distant recurrence risk for avoidance of treatment toxicity and inconvenience that is derived from empirical evidence on patient preferences. While some studies have shown that patients are willing to accept intensive chemotherapy for even a small chance of benefit, individual patients will vary in their preferences and tolerance for adverse effects.

HER2

The human epidermal growth factor receptor (HER) family of receptor tyrosine kinases (EGFR/HER1, ErbB2/HER2, ErbB3/HER3, ErbB4/HER4) plays a major role in the pathogenesis of many solid tumors. In approximately 25% to 30% of breast cancers, overexpression of HER2 has been linked to shorter disease-free (DFS) and overall survival (OS), lack of responsiveness to tamoxifen antiestrogen therapy, and altered responsiveness to a variety of cytotoxic chemotherapy regimens.

Trastuzumab, a monoclonal antibody directed at the extracellular domain of HER2 has offered significant DFS and OS advantages in the metastatic and adjuvant settings in HER2-overexpressing patients, although not all patients respond. Fewer than 50% of patients with metastatic HER2-positive breast cancer show initial benefit from trastuzumab treatment, and many of those eventually develop resistance.[1]

Current methodologies for the selection of HER2-positive patients include immunohistochemistry (IHC) to detect HER2 protein overexpression, and fluorescence in situ hybridization (FISH) to detect HER2 gene amplification. However, controversy still exists regarding the accuracy, reliability, and interobserver variability of these assay methods. IHC provides a semiquantitative measure of protein levels (scored as 0, 1+, 2+, 3+) and the interpretation may be subjective. FISH is a quantitative measurement of gene amplification, in which the HER2 gene copy number is counted. However, FISH, which is considered to be more quantitative analytically, is not always representative of protein expression, and multiple studies have failed to demonstrate a relationship between HER2 gene copy number and response to trastuzumab. Whereas patients who overexpress HER2 protein (IHC) or show evidence of HER2 gene amplification (FISH) have been shown to experience better outcomes on trastuzumab than those scored negative by those assays, differences in the degree of expression or amplification by these methods have generally not been shown to discriminate between groups with different outcomes. IHC and FISH testing may be affected by interlaboratory variability, and neither test provides quantitative data that reflect the activation state of signaling pathways in tumors, which may limit their utility in patient selection.[2] Most laboratories in North America and Europe use IHC to determine HER2 protein status, with equivocal category results (2+) confirmed by FISH (or more recently by chromogenic in situ hybridization [CISH]).

Normally, HER2 activates signaling pathways by dimerizing with ligand-bound EGFR-family members such as HER1 and HER3. A HER2 ligand has not been identified, but overexpressed HER2 is constitutively active. When HER2 is pathologically overexpressed, the receptor may homodimerize and activate signaling cascades in the absence of the normal regulatory control imposed by the requirement for ligand binding of its heterodimerization partners.

A novel assay (HERmark® Breast Cancer Assay; Monogram Biosciences, South San Francisco, CA) was developed to quantify total HER2 protein expression (H2T) and HER2 homodimers (H2D) in formalinfixed, paraffin-embedded tissue samples.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Oncotype DX® and other tests listed herein are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this testing.

In February 2007, MammaPrint® (Agendia) was cleared for marketing by FDA through the 510(k) process. In January 2015, MammaPrint® was cleared for marketing by FDA through the 510(k) process for use in fresh-frozen, paraffin-embedded breast cancer tissue.

In September 2013, Prosigna® was cleared for marketing by FDA through the 510(k) process. FDA determined that Prosigna® was substantially equivalent to MammaPrint®.

Product Code: NYI.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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