Introduction

Breast cancer is a complex disease. Scientists are learning more about breast cancer every year. In the past decade research has shown that measuring certain genes or markers in breast cancer tissue may provide information about prognosis that can be used to make decisions about therapy. Therapies for breast cancer may include surgery, radiation and chemotherapy. The size of the cancer, whether lymph nodes are involved, and what markers or genes are present in the cancer are all factors that are used to select the best treatments for a person with breast cancer. A number of tests are now offered which are specifically for early-stage, hormone-receptor-positive breast cancer. These tests provide an estimate of how likely the cancer is to recur after treatment. Using these tests some women may decide not to have chemotherapy as a treatment when there is a low risk of recurrence. This policy describes when genetic testing to help make decisions about adjuvant treatment after breast cancer surgery may be considered medically necessary and paid for by the health plan. It also describes which tests the plan covers. Some tests need more published studies to show that they accurately describe risk of recurrence, and those tests are considered investigational by the plan, and would not be paid for.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for
providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

### Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medically Necessary Tests:</strong></td>
<td><em>These tests may be considered medically necessary in women with primary, invasive breast cancer meeting ALL of the following characteristics:</em></td>
</tr>
<tr>
<td>- Oncotype DX®</td>
<td>- Unilateral tumor</td>
</tr>
<tr>
<td>- Prosigna®</td>
<td>- Hormone receptor–positive (that is, estrogen receptor [ER]+ (positive), or progesterone receptor [PR]+ (positive))</td>
</tr>
<tr>
<td>- Breast Cancer Index®</td>
<td>- Human epidermal growth factor receptor 2 (HER2)–(negative) (See Table 1 for definitions of IHC and FISH HER2 test results)</td>
</tr>
<tr>
<td>- EndoPredict®</td>
<td>- Tumor size 0.6 to 1 cm with moderate/poor differentiation or unfavorable features OR tumor size larger than 1 cm</td>
</tr>
<tr>
<td>- MammaPrint®</td>
<td>- Node-negative (lymph nodes with micrometastases which are &lt;2 mm in size are considered node negative)</td>
</tr>
<tr>
<td></td>
<td>- The test will be used to decide on the use of chemotherapy to treat the patient’s breast cancer</td>
</tr>
<tr>
<td></td>
<td>- Only one of the tests is covered per individual tumor.</td>
</tr>
<tr>
<td></td>
<td>o In unusual circumstances such as test failure or testing two separate breast cancers, individual consideration is applied.</td>
</tr>
</tbody>
</table>

**The use of these tests for other indications not outlined above are considered investigational, including the following:**

- Determination of recurrence risk in invasive breast cancer patients with positive lymph nodes
- Patients with bilateral breast cancer
- To consider length of treatment with tamoxifen

### Coding
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>0008M</td>
<td>Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score</td>
</tr>
<tr>
<td>81460</td>
<td>Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection</td>
</tr>
<tr>
<td>81465</td>
<td>Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed</td>
</tr>
<tr>
<td>81504</td>
<td>Oncology (tissue of origin), micro-array gene expression profiling of &gt;2000 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as tissue similarity scores</td>
</tr>
<tr>
<td>81519</td>
<td>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</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>S3854</td>
<td>Gene expression profiling panel for use in the management of breast cancer treatment</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

**Related Information**

**Suggested Testing Management**

Unfavorable features that may prompt testing in tumors from 0.6 to 1 cm in size include the following: angiolympathic invasion, high histologic grade, or high nuclear grade.

The 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay Oncotype DX® should not be ordered as a substitute for standard estrogen receptor, progesterone receptor, or human epidermal growth factor receptor 2 (HER2) testing.
The current American Society of Clinical Oncology and College of American Pathologists joint guidelines on HER2 testing in breast cancer (Wolff et al, 2013) has defined positive, negative, and equivocal HER2 test results, as shown in Table 1.

Table 1. ASCO and CAP Definitions of HER2 Test Results (Wolff et al, 2013)

<table>
<thead>
<tr>
<th>Result</th>
<th>Immunohistochemistry</th>
<th>Fluorescence In Situ Hybridization</th>
</tr>
</thead>
</table>
| Negative| 0 or 1+: No staining or faint/barely perceptible, incomplete membrane staining in any proportion of tumor cells | Ratio of HER2/CEP17<sup>a</sup> < 2.0  
AND  
Average HER2 CN < 4.0 signals per cell  
OR  
Average HER2 CN < 4.0 signals per cell<sup>b</sup> |
| Positive| 3+: At least 10% of tumor cells exhibit complete, intense, circumferential membrane staining | Ratio of HER2/CEP17 > 2.0  
OR  
Ratio of HER2/CEP17 is < 2.0  
AND  
Average HER2 CN ≥ 6.0 signals per cell  
OR  
Average HER2 CN ≥ 6.0 signals per cell<sup>b</sup> |
| Equivocal| 2+: Circumferential membrane staining that is either:  
incomplete and/or weak/moderate within >10% of tumor cells  
OR  
complete and intense within ≤10% of tumor cells | Ratio of HER2/CEP17 < 2.0  
AND  
Average HER2 CN ≥ 4.0 and < 6.0 signals per cell  
OR  
Average HER2 CN ≥ 4.0 and < 6.0 signals per cell<sup>b</sup> |

ASCO: American Society of Clinical Oncology; CAP: College of American Pathologists; CEP: chromosome enumeration probe; CN: copy number; HER2: human epidermal growth factor receptor 2.

<sup>a</sup> CEP 17 is a centromeric probe for chromosome 17 (internal control probe).

<sup>b</sup> Signals per cell for test systems without an internal central probe.

Evidence Review
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). This report summarizes the evidence of 5 tests for 4 indications and is organized by indication.

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 (ie, 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 (eg, 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. 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 2. 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 (1-3 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 5 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 For Breast Cancer

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td>Genomic Health (Redwood City, CA)</td>
<td>21-gene RT-PCR</td>
</tr>
<tr>
<td>EndoPredict</td>
<td>Sividon Diagnostics (acquired by Myriad [Salt Lake City, UT] in 2016)</td>
<td>12-gene real-time RT-PCR</td>
</tr>
</tbody>
</table>
# 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 10-year distant recurrence rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the policy. 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. This test is considered medically necessary and is covered when patients meet the criteria.

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 1 study with outcomes in node-negative patients. Although the study showed a low risk of 10-year distant recurrence in patients classified at both low clinical risk and low genetic risk, the study was small and was of moderate-quality data sources. A 2016 study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. A group that may ultimately be identified as having sufficiently low absolute risk is the group at clinical low risk and MammaPrint low risk, which at 5 years had a low absolute risk of distant recurrence of 2.4%. This test is considered medically necessary and is covered when patients meet criteria.

Intrinsic Subtype Classifiers (BluePrint® and TargetPrint®)

The 80-gene expression assay BluePrint® discriminates 3 breast cancer molecular subtypes, and TargetPrint® is a method to measure estrogen receptor (ER), progesterone receptor (PR), and HER2 as an alternative to IHC and FISH. Available evidence is insufficient to determine that BluePrint® and TargetPrint® improve the net health outcome in women with early-stage, invasive breast cancer. Clinical utility of BluePrint® is unknown, because it is unclear how this test will add to treatment decision making using currently available, accepted methods (eg, clinical and pathologic parameters). The incremental benefit of using TargetPrint® as an alternative to current standard methods of measuring ER, PR, and HER2 has not been demonstrated, nor is it included in recommendations for testing issued by the American Society of Clinical Oncology and the College of American Pathologists. These tests are considered investigational at this time, and are not covered.
**EndoPredict**

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 3 prospective-retrospective studies and observational studies. The studies showed that a low score was associated with a low absolute risk of 10-year distant recurrence. Over half of patients in the studies were classified at low risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. This test is considered medically necessary and is covered when patients meet the criteria.

**Breast Cancer Index**

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the Breast Cancer Index (BCI), the evidence includes findings from 2 prospective-retrospective studies and 1 registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk BCI score is associated with low 10-year distant recurrence rates. The findings from the registry-based observational study also showed low 10-year distant recurrence rates. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. This test is considered medically necessary and is covered when patients meet the criteria.

**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 2 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. This test is considered medically necessary and is covered when patients meet the criteria.
Early-Stage Node-Positive Invasive Breast Cancer

For this indication, Oncotype DX and MammaPrint have been evaluated.

21-Gene Assay (Oncotype DX)

For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), the evidence includes clinical trials and prospective-retrospective studies. Although studies showed that Oncotype DX stratifies node-positive patients into high and low risks, it is still uncertain that the risk of disease recurrence is sufficiently low to avoid chemotherapy. Studies have suggested that treatment benefit in chemotherapy is restricted to high-risk patients. The evidence supporting this treatment interaction should be more robust to consider avoiding otherwise currently recommended treatment in patients not at low risk of recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes. This test is considered investigational at this time, and is not covered.

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 (eg, 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. This test is considered investigational at this time, and is not covered.

Ductal Carcinoma in Situ

The Oncotype DX Breast DCIS Score is the only assay investigated for patients with ductal carcinoma in situ (DCIS).

For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS assay, the evidence includes prospective-retrospective studies and prospective trials. Although studies have shown that the test stratifies patients into
high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in patients identified with Oncotype DX Breast DCIS Score is low enough to consider changing the management of DCIS. The evidence is insufficient to determine the effects of the technology on health outcomes. This test is considered investigational at this time, and is not covered.

**Continuation of Tamoxifen Therapy beyond Five Years**

For this indication, EndoPredict, BCI, and Prosigna have been evaluated.

**EndoPredict**

For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 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. This test is considered investigational at this time, and is not covered.

**Breast Cancer Index**

For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with BCI, the evidence includes 2 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. This test is considered investigational at this time, and is not covered.
Prosigna

For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with the Prosigna, the evidence includes two studies from previously conducted clinical trials. The studies 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. This test is considered investigational at this time, and is not covered.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Guidelines from the National Comprehensive Cancer Network (NCCN; v.2.2016) recommend the use of the 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay for determining the use of adjuvant chemotherapy in patients with the following tumor characteristics:

- Hormone receptor-positive (estrogen receptor positive (ER +) and progesterone receptor positive (PR +))
- HER2-negative; [human epidermal growth factor receptor 2]-negative
- Ductal, lobular, mixed, or metaplastic histology
- pT1, pT2, or pT3 stage; and pN0 or pN1mi (≤2 mm axillary node micro-metastasis)
- Tumor >0.5 cm

The guidelines also state: “The 21-gene RT-PCR assay recurrence score can be considered in select patients with 1-3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy.”

Further, the NCCN guidelines state: “The NCCN Panel members acknowledge that many assays have been clinically validated for prediction of prognosis. However, based on the currently available data, the panel believes that the 21-gene assay has been best validated for its use as a prognostic test as well as in predicting who is most likely to respond to systemic chemotherapy.”
Other tests mentioned and studies reviewed in the NCCN guidelines include MammaPrint and Prosigna. NCCN guidelines state that although “Other prognostic multigene assays may be considered to help assess risk of recurrence […], they] have not been validated to predict response to chemotherapy.”

**American Society of Clinical Oncology**

In 2016, the American Society of Clinical Oncology updated its guidelines on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early stage invasive breast cancer. Table 3 shows the gene expression profiling biomarkers found to have clinical utility to guide decisions on the need for adjuvant systemic therapy in this population. The guidelines did not endorse the use of any test for node-positive breast cancer and did not endorse any test for decision making regarding determining the length of tamoxifen treatment.

**Table 3. ASCO Guidelines for Estrogen and Progesterone Receptor-Positive, HER2-Negative, and Node-Negative Breast Cancer**

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
<th>Evidence Type</th>
<th>Evidence Quality</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td>Clinician may use the 21-gene recurrence score to guide decisions on adjuvant systemic chemotherapy</td>
<td>Evidence based</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>EndoPredict</td>
<td>Clinician may use the 12-gene risk score to guide decisions on adjuvant systemic chemotherapy</td>
<td>Evidence based</td>
<td>Intermediate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Breast Cancer Index</td>
<td>Clinician may use the Breast Cancer Index to guide decisions on adjuvant systemic therapy</td>
<td>Evidence based</td>
<td>Intermediate</td>
<td>Moderate</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>Clinician should not use the 70-gene assay to guide decisions on adjuvant systemic therapy</td>
<td>Evidence based</td>
<td>Intermediate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Prosigna</td>
<td>Clinician may use the PAM50 risk of recurrence score, in conjunction with other clinicopathologic</td>
<td>Evidence based</td>
<td>High</td>
<td>Strong</td>
</tr>
</tbody>
</table>
St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer

The 2015 St. Gallen expert panel focused on “providing a practical approach to the allocation of available therapies” based on tumor factors, such as hormone receptors, HER2 status, and metastatic potential as reflected in measures of proliferation and anatomic extent of disease, and patient factors, such as menopausal status, age, comorbidity and patient preference.⁴⁵

For prognosis, the Panel considered the role of multiparameter molecular marker assays separately in years 1 to 5 and beyond 5 years. “Oncotype DX®, MammaPrint®, PAM-50 ROR® score, EndoPredict®, and the Breast Cancer Index® were all considered usefully prognostic for years 1-5. Beyond 5 years, the Panel was divided almost equally on the prognostic value of Oncotype DX®, EndoPredict®, and the Breast Cancer Index®…. PAM50 ROR® score was agreed to be clearly prognostic beyond 5 years, and a clear majority rejected the prognostic value of MammaPrint® in this time period. Only Oncotype DX® commanded a majority in favor of its value in predicting the usefulness of chemotherapy.

The Panel noted that threshold values for decision making about cytotoxic chemotherapy in patients with luminal disease had not been established for any of the tests: “Multi-parameter molecular assays are expensive and therefore unavailable in much of the world.”⁴⁵

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

In November 2014, Palmetto GBA issued a local coverage determination for the Breast Cancer Index.⁴⁶ Effective October 1, 2015, the policy limits coverage of the Breast Cancer Index to patients who meet the following criteria:
• Post-menopausal female with non-relapsed, ER+ breast cancer; and
• Is lymph node negative, and
• Is completing 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).

**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 test.

MammaPrint® was U.S. Food and Drug Association (FDA)–approved on February 6, 2007. MammaPrint® is performed in Agendia laboratories in the Netherlands and in California. On January 23, 2015, MammaPrint® received FDA 510(k) marketing clearance for use in fresh-frozen, paraffin-embedded breast cancer tissue.

Prosigna® received 510(k) clearance from FDA based on substantial equivalence to MammaPrint® on September 6, 2013.

Product Code: NYI.

Other tests mentioned in this policy are offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA)–licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories
offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high-complexity testing.

References


51. Viale G, Slaets L, Bogaerts J, et al. High concordance of protein (by IHC), gene (by FISH; HER2 only), and microarray readout (by TargetPrint) of ER, PgR, and HER2: results from the EORTC 10041/BIG 03-04 MINDACT trial. Ann Oncol. Apr 2014; 25(4):816-823. PMID 24667714


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/14/04</td>
<td>Add to Pathology/Laboratory - New Policy.</td>
</tr>
<tr>
<td>08/09/05</td>
<td>Replace policy - Policy updated with February 2005 TEC Assessment; policy statement wording changed for clarification; indications added to policy guidelines in case of exception being considered.</td>
</tr>
<tr>
<td>01/10/06</td>
<td>Replace policy - Policy updated with reference correction by adding Paik et al 2004 study (cited in TEC Assessment); S code added. No change to policy statement. Presenting to OAP 2/16/06.</td>
</tr>
<tr>
<td>09/12/06</td>
<td>Replace policy - Policy reviewed with literature search; reviewed and recommended by OAP for adoption on 7/25/06; no change in policy statement.</td>
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<tr>
<td>06/12/07</td>
<td>Replace policy - Policy updated with literature review; reference added. No changes in policy statement. Reviewed and recommended by OAP on May 24, 2007.</td>
</tr>
<tr>
<td>07/10/07</td>
<td>Cross Reference Update - No other changes.</td>
</tr>
<tr>
<td>03/11/08</td>
<td>Replace policy - Policy updated with literature review; references and text block for each section was extensively revised. Policy statement changed to indicate that use of Oncotype DX to determine recurrence risk for women who meet specific criteria may be considered medically necessary. Other indications for Oncotype DX or use of other gene expression markers are considered investigational. Reviewed and recommended by OAP on February 21, 2008.</td>
</tr>
<tr>
<td>05/13/08</td>
<td>Cross Reference Update - No other changes</td>
</tr>
<tr>
<td>11/11/08</td>
<td>Replace policy - Policy updated with literature search. Policy statement updated to</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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</tr>
<tr>
<td>01/12/10</td>
<td>Replace policy - Policy updated with literature search. Policy statement added regarding Theros Breast Cancer Index and clarification regarding investigational status for lymph node-positive patients. References added.</td>
</tr>
<tr>
<td>03/09/10</td>
<td>Cross Reference Update - No other changes</td>
</tr>
<tr>
<td>09/14/10</td>
<td>Replace policy - Policy updated with literature review. The policy statement has been updated to include Mammostrat and Aviara MGI. Reviewed and recommended by OAP on August 19, 2010.</td>
</tr>
<tr>
<td>08/09/11</td>
<td>Replace policy – Policy updated with literature search; rationale revised extensively. Reference numbers 1, 4, 5, 16-24, 26, 29, 30, 32, 42-46, 53, 56-59, 61 added; no change to policy statements. ICD-10 codes added to policy.</td>
</tr>
<tr>
<td>04/16/12</td>
<td>Related Policies updated: policies 2.01.45, 2.01.55 and 7.01.09 removed, as these policies have been archived.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.36 (previously 2.04.36) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>07/25/12</td>
<td>Update Related Policies – 2.04.37 has been added.</td>
</tr>
<tr>
<td>12/11/12</td>
<td>Replace policy. Policy updated with new statement that use of the 21-gene RT-PCR assay (Oncotype DX) test for patients with bilateral disease is considered investigational. NexCourse® Breast IHC4 is a new test that is added as investigational. Policy guidelines include information under the header of “Testing Management” that is moved from the policy section for usability. Rationale updated with literature review through October 2012. Reference numbers 24, 26, 27, 44, 46, 47, 59, 64-67, 70, 72-76 added, others renumbered or removed. Policy statement changed as noted. Remove Related Policies 6.01.510 and 8.01.516 as they were archived.</td>
</tr>
<tr>
<td>01/10/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT code 81200 – 81479 and 81599, effective 1/1/13, added to the policy.</td>
</tr>
<tr>
<td>02/11/13</td>
<td>Replace policy. Policy statement updated with addition of “ALL” of the following criteria. Added Oncotype DX™ DCIS is investigational. Rationale reorganized and updated with DCIS study information. Retained the Policy guidelines header of “Testing Management” that includes criteria moved from the policy section for usability. References renumbered or removed to match the rationale section revision. ICD-9 233.0 and ICD-10 D05.00-D05.92 added to codes table. Policy statement changed as noted.</td>
</tr>
<tr>
<td>12/23/14</td>
<td>Coding Update. Add CPT 81504, effective 01/01/14; 83890-838913 removed as they are now deleted; code range 81200 – 81479 removed.</td>
</tr>
<tr>
<td>04/14/14</td>
<td>Interim update. Medical necessity criteria of treatment with adjuvant therapy (eg,</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
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</tr>
<tr>
<td>tamoxifen or aromatase inhibitors) removed. Blue-Print and TargetPrint tests incorporated into the policy; references 82 and 83 added.</td>
<td></td>
</tr>
<tr>
<td>09/08/14</td>
<td>Annual Review. Policy updated with literature review through June 14, 2014. References 2, 15-16, 26-28, 37, 39, 44, 47-50, 53-55, 62-67, 76, 85-88, and 92-98 added; references 1, 12, and 106 updated; reference 2-4 and 32 deleted. Policy statement changed to include newer assays BreastPRS, EndoPredict™, BluePrint® and TargetPrint® as investigational. Policy statement on PAM50 updated to Prosigna™. Policy statement added that the use of gene expression assays in men with breast cancer is considered investigational.</td>
</tr>
<tr>
<td>01/01/15</td>
<td>Coding update. New CPT codes 81440, 81465 and 81519, effective 1/1/15, added to policy.</td>
</tr>
<tr>
<td>09/08/15</td>
<td>Annual Review. Policy updated with literature review through June 3, 2015; references 29-33, 37, 43, 71-72, 74, 77, 90, 102-105, 108-109, 117, 121-122, and 126 added; references 90-91 deleted; reference 124 updated. Policy statements unchanged. Policy continues to be formatted as described on 02/11/13.</td>
</tr>
<tr>
<td>08/01/16</td>
<td>Update Related Policies. Remove 2.04.37 as it was deleted and content moved to 2.04.141.</td>
</tr>
<tr>
<td>08/09/16</td>
<td>Update Related Policies. Remove 8.01.27 as it was archived.</td>
</tr>
<tr>
<td>11/08/16</td>
<td>Minor update. Language added to clarify that this policy addresses gene expression profiling in women. No peer reviewed published medical literature on the use of gene expression profiling in men with breast cancer has been identified. No change in policy statements.</td>
</tr>
<tr>
<td>03/01/17</td>
<td>Annual Review, approved February 14, 2017. Policy updated with literature review through October 10, 2016. Reorganized by indication rather than test. Policy statement revised: EndoPredict, Breast Cancer Index, Mammaprint and Prosigna, previously considered investigational, are medically necessary for same indications as Oncotype DX. Other statements revised to reflect these tests investigational for other indications. Note added that only one of these tests is covered per individual tumor, unless unusual circumstances warrant. Statement of BluePrint and TargetPrint as investigational retained. Tests that are no longer commercially available (NexCourse, BreastPRS, Mammostrat and BreastOncPx) removed from policy. References 7, 11, 14-16, 31, 43-44 and 48-52 added; note 46 updated; several references removed. Removed Appendix table.</td>
</tr>
<tr>
<td>04/18/17</td>
<td>Policy moved into new format; no change to policy statements.</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Interim review, approved June 22, 2016. Minor clarification to policy statement. Changed from &quot;and&quot; to &quot;or&quot; for Hormone receptor.</td>
</tr>
</tbody>
</table>
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5992. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Ilkuu (Illoko):
Daytoy a Pakdaak ket naglaon iti Napateg nga Impomarson. Daytoy a pakdaak maraalin nga adda ket naglaon iti napeaye nga impomarson maipanggep iti aplsakonyono wenno coverage babaen iti Premera Blue Cross. Daytoy ket maraalin dagiit importante a petaa iti daytoy a pkaadarr. Maraalin nga adda rumbeng nga aramidemoo nga adda sakbay dagiit partuklu a naituding nga adda aldaw tapno mappatgaalindeeyo ti tagee ti salu-apii wenno tulgong kadagit gastos. Adda karbenganyo a mangala iti daytoy nga impomarson ken tulgong iti bukodyo a paggasao nga awan ti bayadanyoo. Tumawag ti numero nga osa 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
This notification may contain important information about your claim or coverage. Certain portions of this notice may be translated into different languages. **English:** If you have a request or claim that you believe is not correct, you may file a complaint with Premera Blue Cross. To file a complaint, you may contact Premera Blue Cross by calling 800-722-1471 (TTY: 800-842-5357) or writing to us at:

Premera Blue Cross
PO Box 3535
Olympia, WA 98507-2715

**Other Languages:** This notice also contains important information about your health care. If you have any questions, please call 800-722-1471 (TTY: 800-842-5357) or visit our website (Premera.com) for more information.

**Premera Blue Cross:**

800-722-1471 (TTY: 800-842-5357)

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**Japanese (Japanese):**

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**Korean (Korean):**

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross를 통한 커버리지에 관한 정보를 포함하고 있습니다. 본 통지서에는 독성이 있는 날짜들이 있을 수 있습니다. 귀하의 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보는 정부의 안전과 비용 부담없이 얻을 수 있는 권리가 있습니다。800-722-1471 (TTY: 800-842-5357)로 전화하시오.

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**Romanian (Romanian):**


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**Russian (Russian):**

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

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**Tagalog (Tagalog):**

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay naglalaman ng mahalagang impormasyon.

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**Ukrainian (Ukrainian):**

Це повідомлення містить важливу інформацію. Цей повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).

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**Vietnamese (Vietnamese):**


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