MEDICAL POLICY – 12.04.36
Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

BCBSA Ref Policy: 2.04.36
Effective Date: May 1, 2018
Last Revised: Nov. 17, 2018
Replaces: 2.04.36
RELATED MEDICAL POLICIES: None

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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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 the 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</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-Gene reverse transcriptase polymerase chain reaction (RT-PCR)</td>
<td>These tests may be considered medically necessary to determine recurrence risk in women with primary, invasive breast cancer meeting ALL of the following characteristics:</td>
</tr>
<tr>
<td>assay:</td>
<td>• Unilateral tumor</td>
</tr>
<tr>
<td></td>
<td>• Hormone receptor–positive (that is, estrogen receptor [ER]+ (positive), or progesterone receptor [PR]+ (positive))</td>
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<tr>
<td></td>
<td>• Human epidermal growth factor receptor 2 (HER2)–(negative)</td>
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<td></td>
<td>• Tumor size 0.6 to 1 cm with moderate/poor differentiation or unfavorable features OR tumor size larger than 1 cm</td>
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<tr>
<td></td>
<td>• Node-negative (lymph nodes with micrometastases which are &lt;2 mm in size are considered node negative)</td>
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<td>• The individual will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors)</td>
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<td>• The test will be used to decide on the use of chemotherapy to treat the patient’s breast cancer (when chemotherapy is a therapeutic option)</td>
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<td>• The test is ordered within 6 months after diagnosis</td>
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<td>• Only one of the tests is covered per individual tumor</td>
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<tr>
<td></td>
<td>o In unusual circumstances such as test failure or testing two separate breast cancers, individual consideration is applied</td>
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<tr>
<td></td>
<td>The use of these tests for other indications not outlined above are considered investigational, including but not limited to the following:</td>
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<tr>
<td></td>
<td>• Determination of recurrence risk in invasive breast cancer patients with positive lymph nodes</td>
</tr>
</tbody>
</table>
### Test | Medical Necessity
---|---
- Predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (ie, Oncotype DX® DCIS)
- Patients with bilateral breast cancer
- The use of gene expression assays in men with breast cancer
- To consider length of treatment with tamoxifen

### Test | Investigational
---|---
**MammaPrint®**
**BluePrint®**  | Use of 70 gene signature (MammaPrint®) for any indication is considered investigational.
  
  The use of BluePrint® in conjunction with MammaPrint® or alone is considered investigational.
  
**TargetPrint®**  | Use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (eg, TargetPrint®) is considered investigational.
  
**Other gene expression assays**  | The use of other gene expression assays (Mammostrat® Breast Cancer Test, BreastOncPx™, NexCourse® Breast IHC4, BreastPRS™) for any indication is considered investigational.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT</strong></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 (Prosigna) (code terminated 1/1/18)</td>
</tr>
<tr>
<td>0045U</td>
<td>Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score (new code effective 7/1/18)</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</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</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 (Oncotype DX)</td>
</tr>
<tr>
<td>81520</td>
<td>Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score (new code effective 1/1/18)</td>
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<tr>
<td>81521</td>
<td>Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis (new code effective 1/1/18)</td>
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</tbody>
</table>

**HCPCS**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<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

**Note About Testing**

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.
Suggested Testing Management

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 (ie, 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 when the test result will aid in making decisions regarding chemotherapy.

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

Unfavorable features that may prompt testing in tumors from 0.6 to 1 cm in size include the following: angiolymphatic 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/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.

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), or to recommend extended endocrine therapy in patients who are recurrence-free at 5 years. This report summarizes the evidence of 5 tests, which are organized by indication: Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna.
Background

Newly Diagnosed Breast Cancer

Most women with newly diagnosed breast cancer in the United States present with early-stage or locally advanced (ie, nonmetastatic) disease. However, almost a third of women who are disease-free after initial local and regional treatment develop distant recurrences during follow-up. Current breast cancer treatment regimens involve systemic adjuvant chemotherapy, hormonal therapy, biologic therapy, or a combination of these, depending on the patient’s baseline level of recurrence risk, hormonal markers, and risk tolerance.

Women whose tumors are positive for human epidermal growth factor receptor 2 (HER2) should receive adjuvant therapy with a HER2-directed therapy (trastuzumab with or without pertuzumab). Decision making about using adjuvant biologic therapy for women with HER2-positive cancer is not discussed here. This policy focuses on the use of genetic testing to help determine the prognosis of women with hormone receptor positive, HER-2 negative breast cancer

Selection of Adjuvant Chemotherapy Based on Risk of Recurrence

An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant cytotoxic chemotherapy. 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 the patients’ baseline prognosis. However, the absolute benefit of chemotherapy depends on the underlying or baseline risk of recurrence. Women with the best prognosis have tumors that are small, early-stage, estrogen receptor–positive, and lymph node negative. Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy. These women have an approximately 15% ten-year risk of recurrence with tamoxifen alone; approximately 85% of these patients could avoid the toxicity of adjuvant cytotoxic 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 number of affected lymph
nodes. Consensus guidelines for defining receptor status exist. However, no single classifier is considered a criterion standard. As a result, a substantial number of patients are treated with chemotherapy who fail to benefit. Better predictors of recurrence risk could help women’s decision making, some of whom may prefer to avoid chemotherapy if assured their risk is low.

**Selection of Extended Endocrine Therapy**

Randomized controlled trials have established that 5 years of tamoxifen improves mortality in women with hormone receptor-positive breast cancer. A 2011 individual patient data meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group, including 20 trials (total N=21,457 patients) found that 5 years of tamoxifen in estrogen receptor–positive disease reduced the risk of recurrences by almost 50% over 10 years on the relative scale; breast cancer mortality was decreased by 29% through 15 years.

For patients with early-stage, invasive breast cancer that is hormone receptor-positive, the use of endocrine therapy (tamoxifen and/or an aromatase inhibitor, with or without ovarian suppression) for 5 to 10 years following initial diagnosis has support in national guidelines. However, the regimens available and the evidence to support them vary.

Randomized controlled trials published recently have shown that extended endocrine therapy decreases the risk of recurrence. The American Society for Clinical Oncology and the National Comprehensive Cancer Network guidelines were informed primarily by results of the ATLAS trial, which compared 5 and 10 years of tamoxifen and the subsequent aTTom trial (reported in abstract form). In both trials, in women who were hormone receptor-positive and had completed 5 years of tamoxifen, 5 years of extended tamoxifen was associated with improvements in breast cancer-specific mortality; ATLAS showed improvements in overall survival.

Three previously reported randomized trials of extended tamoxifen treatment had mixed findings: Tormey et al (1996; total N=194 patients), the National Surgical Adjuvant Breast and Bowel Project (Fisher et al, 2001; total N=1172 patients), and the Scottish Cancer Trials Breast Group (Stewart et al, 2001; total N=342 patients).

Overall, the available trial evidence would suggest that 10 years of tamoxifen in pre- or postmenopausal women can be linked with improved survival while trials of extended aromatase inhibitors in different populations of hormone receptor-positive patients have had more mixed results.
In addition to the trials published in full-length form, 3 trials were presented in early 2017 evaluating extended endocrine therapy in postmenopausal women (NSABP-42 [NCT00382070]: 10 years vs 5 years of letrozole; DATA [NCT00301457]: 6 years vs 3 years of anastrozole; and IDEAL [NTR3077] 10 years vs 7.5 years of letrozole) did not meet their primary end points.

**Clinical Uses of Gene Expression Signatures for Breast Cancer**

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 policy 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 policy:

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, hormone receptor-positive, 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 1. Gene Expression Tests Reporting Recurrence for Breast Cancer Considered Herein

<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>
<tr>
<td>Breast Cancer Index®Prognostic</td>
<td>bioTheranostics (San Diego, CA)</td>
<td>Combines MGI and the HOXB13:IL17BR Index measured using RT-PCR</td>
</tr>
<tr>
<td>MammaPrint®</td>
<td>Agendia (Amsterdam, The Netherlands)</td>
<td>70-gene DNA microarray</td>
</tr>
<tr>
<td>Prosigna®</td>
<td>NanoString Technologies (Seattle, WA)</td>
<td>Gene-expression profile is assessed by the nCounter® digital platform system to determine similarity with prototypic profiles of PAM50 genes for breast cancer</td>
</tr>
</tbody>
</table>

MGI: Molecular Grade Index; PAM50: prediction analysis of microarray 50 gene set; ROR: risk of relapse, RT-PCR: reverse transcriptase polymerase chain reaction, EP: expression profile.

Additional commercially available tests may provide some prognostic or predictive information for breast cancer. TargetPrint® (Agendia) is a microarray-based gene expression test that offers a quantitative assessment of ER, PR, and HER2 overexpression in breast cancer. The test is marketed to be used in conjunction with MammaPrint® and BluePrint®.

Other commercially available biomarkers are designed to provide information about tumors’ molecular subtypes (ie, luminal A, luminal B, HER2 type, and basal type). Prosigna was initially offered as a molecular subtype test. BluePrint® is an 80-gene expression assay that classifies breast cancer into basal type, luminal type, or HER2-type. The test is marketed as an additional stratifier into a molecular subtype after risk assessment with MammaPrint® to augment predictive data about response to chemotherapy.
Summary of Evidence

*Early-Stage Node-Negative Invasive Breast Cancer*

For the evaluation of breast cancer-related gene expression profiling tests for the management of all early-stage breast cancer populations, study populations considered had positive hormone receptor status, and negative HER2 status. Studies retrospectively collecting tumor samples from prospective trials that provided 10-year distant recurrence rates or 10-year survival rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the policy.

**Oncotype DX (21-Gene Assay)**

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the Oncotype DX (21-gene assay), 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, 3%-7%; upper bound of the 95% confidence intervals, 6% to 10%). 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.

**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 revealed that a low score was associated with a low absolute risk of 10-year distant recurrence. (average risk at 10 years for the two larger studies, 3%-6%, upper bound of the 95% confidence interval, 6% to 9%). 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.
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, 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 Breast Cancer Index score is associated with low 10-year distant recurrence rates (average risk at 10 years, 5%-7%, upper bound of the 95% confidence interval, 8% to 10%). 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.

MammaPrint (70-Gene Signature)

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 prospective-retrospective study and a study using a cancer registry cohort. The prospective-retrospective study reported high 10-year distant metastases-free survival for the low-risk group treated with tamoxifen (93%; 95% CI, 88% to 96%), but not as high survival for the low-risk group not treated with tamoxifen (83%, 95% CI, 76% to 88%). Although the registry study showed a low risk of 10-year distant recurrence, the source is not considered high-quality. A recently reported study of clinical utility only reported 5-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 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 (average risk at 10 years, 3%-5%, upper bound for the study providing confidence interval, 6%). 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**

For decisions on management of early-stage node-positive disease, Oncotype DX, EndoPredict, MammaPrint, and Prosigna were evaluated. Only studies presenting 10-year distant recurrence rates or 10-year survival rates were included in this part of the policy.

**Oncotype DX (21-Gene Assay)**

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the Oncotype DX (21-gene assay), the evidence includes 2 prospective-retrospective studies and one prospective study. The prospective-retrospective studies showed that Oncotype DX stratifies node-positive patients into high and low risk for distant recurrence-free survival. However, only one of the studies reported CIs for estimates and those are very wide. The prospective study included patients with node-negative and node-positive breast cancer. The authors reported that subgroup analyses of patients with node-positive breast cancer who were classified as low risk experienced higher rates of survival than patients classified as high risk, though no rates were provided. There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy, but accurate risk estimates are needed to inform patient decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

**EndoPredict**

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 2 prospective-retrospective analyses. In a study the 10-year distant recurrence rate in low-risk EPclin score patients was estimated to be 5% (95% confidence interval, 1% to 9%). In the other study, 10-year distant recurrence rate in low-risk EPclin score patients was estimated to be 5%, but the upper bound of the 95% CI was close to 20%. To establish that the test has potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision-making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.
MammaPrint (70-Gene Signature)

For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the MammaPrint (70-gene signature), the evidence includes a clinical utility study and an observational study. The study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. The observational study reported that the low-risk group experienced a low rate of 10-year distant recurrence; however, the standard error around the rate did not meet the threshold benefit of less than 10%. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

Prosigna

For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the Prosigna ROR score, the evidence includes a single prospective-retrospective study. The 10-year distant recurrence rate in low-risk Prosigna ROR patients with a single positive node is roughly two-fold the rate in low-risk ROR score node-negative patients. However in the single available study, the upper bound of the 95% confidence interval for 10-year distant recurrence in node-positive patients classified as ROR score low-risk was about 13%, which approaches the range judged clinically informative in node-negative patients. The predicted recurrence rates require replication. To establish that the test has potential for clinical utility, it should be able to identify a low-risk group with a...
recurrence risk that falls within a range that is clinically meaningful for decision making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ductal Carcinoma in Situ**

**Oncotype DX Breast Score**

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 Score, the evidence includes a prospective-retrospective study and a retrospective cohort study. Although the 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..

**Extended Endocrine Therapy**

For this indication, Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint and Prosigna were evaluated. Studies retrospectively collecting tumor samples from prospective trials that provided 10-year distant recurrence rates or 10-year survival rates were included in this part of the policy. Studies comparing genetic assays with clinical risk prediction tools were also included.

**Oncotype DX (21-Gene Assay)**

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes a study from a previously conducted clinical trial. The study did not show low distant recurrence rates in patients classified as low risk with the test, and no confidence intervals were presented. The
ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

**EndoPredict**

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are 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 as low risk with EndoPredict. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Additional prospective trials or retrospective-prospective studies of archived samples reporting on the association between risk score and survival are needed for confirmation of results from the single study. More importantly, clarity is needed about how the test would inform clinical practice. 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 who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with the Breast Cancer Index, the evidence includes 3 analyses of archived tissue samples from two previously conducted clinical trials and a retrospective cohort study. The analyses showed low distant recurrence rates in patients classified as low risk with the test. Two studies suggested that, in addition to having a more favorable prognosis, low-risk patients may receive less benefit from extended endocrine therapy. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effect of the technology on health outcomes.

**MammaPrint (70-Gene Signature)**

For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a
retrospective-prospective study. Analyses on patients classified as ultralow risk (a subgroup of the low-risk group) showed that this ultralow-risk group experienced high 10- and 20-year breast cancer-specific survival rates. Additional studies are needed to confirm the results of this single study. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. 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 who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with Prosigna, the evidence includes 2 studies from previously conducted clinical trials examined in 3 publications. The studies showed low distant recurrence rates in patients classified as low risk with the test. A reclassification result suggested that the test may offer little improvement over clinical predictors alone. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effect of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in **Table 2**.

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01501487</td>
<td>MINT: Multi-Institutional Neo-Adjuvant Therapy MammaPrint Project</td>
<td>226</td>
<td>Jun 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT00310180</td>
<td>Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning Individualized Options for Treatment: The TAILORx Trial71</td>
<td>11,248</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02627703</td>
<td>A Prospective Clinical Utility Study of the Impact of the 21-</td>
<td>80</td>
<td>Dec 2017</td>
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<tr>
<td>NCT No.</td>
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<td>Planned Enrollment</td>
<td>Completion Date</td>
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<tr>
<td>NCT02395575</td>
<td>Gene Recurrence Score Assay (Oncotype DX) in Estrogen Receptor Positive (ER+) HER 2 Negative (HER2-) 1-3 Node Positive (pN1) Breast Cancer in Multiple BC Cancer Agency Centres</td>
<td></td>
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<tr>
<td>NCT00433589</td>
<td>Prospective Study Evaluating the Clinical Impact of the Breast Cancer Intrinsic Subtype-Prosigna Test (Assay) in the Management of Early Stage Breast Cancers</td>
<td>200</td>
<td>Dec 2017</td>
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<tr>
<td>NCT02653755</td>
<td>MINDACT (Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy): A Prospective, Randomized Study Comparing the 70-Gene Signature With the Common Clinical-Pathological Criteria in Selecting Patients for Adjuvant Chemotherapy in Breast Cancer With 0 to 3 Positive Nodes</td>
<td>6600</td>
<td>Mar 2020</td>
</tr>
<tr>
<td>NCT01272037</td>
<td>A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients With 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer With Recurrence Score (RS) of 25 or Less. RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer</td>
<td>10,000</td>
<td>Feb 2022</td>
</tr>
<tr>
<td>NCT02400190</td>
<td>The IDEA Study (Individualized Decisions for Endocrine Therapy Alone)</td>
<td>200</td>
<td>Mar 2026</td>
</tr>
</tbody>
</table>

NCT: National clinical trial  
*a* Denotes industry-sponsored or cosponsored trial

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

Guidelines from the National Comprehensive Cancer Network (NCCN; v.2.2017) 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. A retrospective analysis of a prospective randomized trial suggests that the test is predictive in this group similar to its performance in node-negative disease”

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 “Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy.”

**American Society of Clinical Oncology**

In 2017, the American Society of Clinical Oncology updated its evidence-based 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 demonstrated clinical utility to guide decisions on the need for adjuvant systemic therapy in women with early-stage invasive breast cancer and known estrogen and progesterone and HER2 status. The guidelines did not endorse the use of any test for node-positive breast cancer and did not endorse any test for decision making to determine the length of tamoxifen treatment.
Table 3. Guidelines for Estrogen and Progesterone Receptor-Positive, and HER2-Negative Breast Cancer

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
<th>Evidence Quality</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Node-negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncotype DX</td>
<td>Clinician may use the 21-gene recurrence score to guide decisions on adjuvant systemic chemotherapy</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>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>Intermediate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
| MammaPrint       | • Clinician may use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization  
                  | • Clinician should not use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with low clinical risk per MINDACT categorization | High             | Strong                      |
| Prosigna         | Clinician may use the PAM50 risk of recurrence score, in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy | High             | Strong                      |
| **Node-positive (1-3 nodes)** |                                                                                |                  |                             |
| MammaPrint       | Clinician may use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization | High             | Moderate                    |

HER2: human epidermal growth factor receptor 2.
**European Group on Tumor Markers**

In 2017, the European Group on Tumor Markers updated its guidelines on the clinical use of biomarkers in breast cancer.\(^{68}\) Table 4 summarizes guidelines on the use of biomarkers in patients with invasive breast cancer.

**Table 4. Guidelines on the Use of Biomarkers in Patients with Invasive Breast Cancer**

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
<th>LOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td>1A</td>
<td>A</td>
</tr>
<tr>
<td>Prosigna</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td>EndoPredict</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td>Breast Cancer Index</td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive/HER2-negative, lymph node-negative disease</td>
<td>1B</td>
<td>A</td>
</tr>
</tbody>
</table>

ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; LOE: level of evidence; SOR: strength of recommendation.

**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 the 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.\(^{69}\)
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.69

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.”61

**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.70 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.

In February 2007, MammaPrint® (Agendia) was cleared for marketing by the FDA through the 510(k) process for the prediction of breast cancer metastasis. In January 2015, MammaPrint® was cleared for marketing by the 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 the FDA through the 510(k) process. The FDA determined that Prosigna® was substantially equivalent to MammaPrint®.

FDA product code: NYI.

Currently, the Breast Cancer IndexSM (Biotheranostics) and EndoPredict® (distributed by Myriad) are not FDA-approved.

References


75. 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


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**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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</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>
</tr>
<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 include updated assays (Mammostrat and Aviari MGI) that are considered investigational. References added.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</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>
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<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>12/23/13</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, tamoxifen or aromatase inhibitors) removed. Blue-Print and TargetPrint tests incorporated into the policy; references 82 and 83 added.</td>
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<tr>
<td>Date</td>
<td>Comments</td>
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<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 “and” to “or” for Hormone receptor.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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</tr>
<tr>
<td>12/01/17</td>
<td>Interim Review, approved November 21, 2017. Policy updated with literature review through March 2017. References 1, 6, 8-12, 18-24, 37-42, and 45-50 were added; others removed and/or updated. Medical necessity criterion added to policy statement: test is ordered within 6 month after diagnosis. Additional examples of investigational indications added back in which had been inadvertently removed: determination of recurrence risk of ductal carcinoma in situ; use in men with breast cancer. BluePrint and TargetPrint removed from related information section; they are not within the scope of this policy. No other changes.</td>
</tr>
<tr>
<td>01/23/18</td>
<td>Coding update, added CPT codes 81520, 81521, and 81541 (new codes effective 1/1/18).</td>
</tr>
<tr>
<td>01/30/18</td>
<td>Coding updated, added note that CPT code 0008M was terminated 1/1/18.</td>
</tr>
<tr>
<td>04/13/18</td>
<td>Coding update, removed CPT code 81541.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 17, 2018. Policy updated with literature review through September 2017; some references updated, references 71-75* were added. Policy statement added that MammaPrint, BluePrint, and Target are investigational as well as any other gene expression assays for any indication.</td>
</tr>
<tr>
<td>09/01/18</td>
<td>Minor update. Re-added language clarifying 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; this information was inadvertently removed during a previous update.</td>
</tr>
<tr>
<td>11/17/18</td>
<td>Coding update, added CPT code 0045U (new code effective 7/1/18).</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). ©2018 Premera All Rights Reserved.

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  - Information written in other languages

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200 Independence Avenue SW, Room 509F, HHH Building
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