FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Description
Laboratory tests have been developed to detect the expression, via messenger RNA, of 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 the postsurgical management of breast cancer, 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 for 5 tests, which are organized by indication: Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna.

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

OBJECTIVE
The objective of this evidence review is to determine whether Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna testing improve the net health outcome among women making decisions about breast cancer treatment.

POLICY STATEMENT
The use of the 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay (ie, Oncotype DX) to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive breast cancer meeting all of the following characteristics:

- unilateral tumor;
- hormone receptor positive (i.e., estrogen receptor positive or progesterone receptor positive);
- human epidermal growth factor receptor 2 negative;
- tumor size 0.6 to 1 cm with moderate or poor differentiation or unfavorable features OR tumor size larger than 1 cm;
- node-negative (lymph nodes with micrometastases <=2 mm in size, are considered node-negative for this policy statement);
- who will be treated with adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitors);

Effective Date: April 1, 2019
Related Policies: None
● when the test result aids the patient in deciding on chemotherapy (i.e., when chemotherapy is a therapeutic option); AND
● when ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown.

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

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

Use of EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in women with primary, invasive breast cancer with the same characteristics as considered medically necessary for Oncotype DX.

All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX), EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes, patients with bilateral disease, or to consider the length of treatment with tamoxifen, are considered investigational.

Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX® Breast DCIS Score) to inform treatment planning after excisional surgery is considered investigational.

The use of BluePrint in conjunction with MammaPrint or alone is considered investigational.

Use of gene expression assays in men with breast cancer is considered investigational.

**POLICY GUIDELINES**

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 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.

Current American Society of Clinical Oncology and College of American Pathologists joint guidelines on HER2 testing in breast cancer (Wolff et al 2013,) have defined positive, negative, and equivocal HER2 test results.

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.
Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Table 1. Gene Expression Tests Reporting Recurrence Risk 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</td>
<td>21-gene RT-PCR; identifies 3 groups as low, intermediate, and high risk for distant recurrence</td>
</tr>
<tr>
<td>EndoPredict®</td>
<td>Sividon Diagnostics (acquired by Myriad in 2016)</td>
<td>12-gene real-time RT-PCR; gene expression molecular score alone (EP) or EP is combined with the clinical parameters of tumor size and number positive lymph nodes (EPclin), resulting in classifications of EP low, EP high, EPclin low, or EPclin high risk for distant recurrence</td>
</tr>
<tr>
<td>Breast Cancer IndexSM Prognostic</td>
<td>Biotheranostics</td>
<td>Combines MGI and the HOXB13:IL17BR Index measured using RT-PCR; identifies 2 groups as low or high risk for distant recurrence</td>
</tr>
<tr>
<td>MammaPrint®</td>
<td>Agendia</td>
<td>70-gene DNA microarray; identifies 2 groups as low or high risk for distant recurrence</td>
</tr>
<tr>
<td>Prosigna®</td>
<td>NanoString Technologies</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; identifies 3 categorical ROR groups (ROR-low, ROR-intermediate, ROR-high)</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 prognostic or predictive information for breast cancer. Tests intended to assess estrogen receptor, progesterone receptor, and HER2 status, such as TargetPrint® (Agendia; via quantitative microarray), are outside the scope of this review. In addition, tests that do not provide a specific recurrence risk are outside the scope of this review.
Other commercially available biomarkers are designed to provide information about tumors’ molecular subtypes (i.e., luminal A, luminal B, HER2 type, and basal type). Prosigna was initially offered as a molecular subtype test. The BluePrint® 80-gene molecular subtyping assay is offered in combination with MammaPrint to augment predictive data about response to chemotherapy.

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

In 2007, MammaPrint® (Agendia) was cleared for marketing by the FDA through the 510(k) process for the prediction of breast cancer metastasis. In 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 2013, Prosigna® was cleared for marketing by the FDA through the 510(k) process. Moreover, 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.

**RATIONALE**

**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**

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 provide at least 5-year distant recurrence rates or at least 5-year survival rates in node-negative women were included in this part of the evidence review.

**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 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% CI, 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.
FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

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 2 larger studies, 3%-6%; upper bound of the 95% CI, 6% to 9%). Over half of patients in these 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 BCI, the evidence includes findings from 2 prospective-retrospective studies and a 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 (average risk at 10 years, 5%-7%; upper bound of the 95% CI, 8% to 10%). 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 MammaPrint (70-gene signature), the evidence includes a prospective-retrospective study, a study using a cancer registry cohort, and an RCT providing evidence for clinical utility. The prospective-retrospective study reported high 10-year distant metastasis-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. The RCT (MINDACT) showed 5-year distance recurrence rates below the 10% threshold among patients identified as low risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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 95% CI, 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

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FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with 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 evidence review.

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 Oncotype DX (21-gene assay), the evidence includes 2 prospective-retrospective studies and a 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-negative 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 1 study, the 10-year distant recurrence rate in low-risk EPclin score patients was estimated to be 5% (95% CI, 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 who are considering adjuvant chemotherapy who receive gene expression profiling with 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.

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 twofold the rate in low-risk ROR score node-negative
patients. However, in the single available study, the upper bound of the 95% CI 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**

The Oncotype DX Breast DCIS Score is the only assay investigated for patients with DCIS.

**Oncotype DX Breast DCIS Score**

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 a 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, BCI, 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 evidence review. 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 2 studies using data from the same previously conducted clinical trial. One analysis did not provide CIs and the other study reported a distant recurrence rate of 4.8% (95% CI, 2.9% to 7.9%) for the low-risk group. 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 endocrine treatment who receive gene expression profiling with EndoPredict, the evidence includes 2 analyses of archived tissue samples from 2 previously conducted clinical trials. The studies showed low distant recurrence rates in patients classified as low risk.
FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

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 to confirm 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 effects 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 BCI, 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 and high distant recurrence-free survival 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 effects 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 several 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 effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

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FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Adjuvant Chemotherapy for Node-Negative Breast Cancer

Current guidelines from the National Comprehensive Cancer Network (NCCN) for breast cancer (v.2.2018) provide a summary table assessing multigene assays to inform the addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy (page BINV-M). The table shows that several genetic assays can be used to identify patients with node-negative breast cancer and low recurrence risk scores who may derive little benefit from chemotherapy. The NCCN category of evidence and consensus for the following assays is: level 1 for Oncotype DX and MammaPrint, and level 2A for Prosigna, EndoPredict, and the Breast Cancer Index. In the table, NCCN states that all the tests are prognostic, but only the Oncotype DX is predictive of response to chemotherapy in patients with node-negative breast cancer and is the preferred testing of the Network panel. In addition to the summary table, the following recommendation appears in an updated algorithm:

- "Strongly consider 21-gene RT-PCR assay" for node-negative, ER+ estrogen receptor positive, HER2- human epidermal growth factor receptor 2negative, breast cancer with "pT1, pT2, or pT3; and pN0" and tumor less than 0.5 cm. "Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy."

Adjuvant Chemotherapy for Node-Positive Breast Cancer

The table discussed above in the NCCN guidelines for breast cancer (v.2.2018) also provides information on the use of genetic assays to inform recurrence risk for patients with node-positive (1 to 3 nodes) breast cancer. The level of evidence and consensus for Oncotype DX, MammaPrint, and EndoPredict for this population is 2A. In addition to the summary table, the following recommendation appears in an updated algorithm:

- "Consider multigene assay to assess prognosis and determine chemotherapy benefit" for node-positive, ER+, HER2- breast cancer with "pN1mi (<=2 mm axillary node metastasis) or N1 (<4 nodes). "There are few data regarding the role of multigene assays in women with four or more ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this groups should be based on clinical factors." For N1mi and N1, "multigene assays are prognostic and not proven to be predictive of chemotherapy benefit but can be used to identify a low risk population that when treated with proper endocrine therapy may derive little absolute benefit from 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 2 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 any test for decision-making to determine the length of tamoxifen treatment.

Table 2. Guidelines for Estrogen and Progesterone Receptor Positive and HER2-Negative Breast Cancer

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FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

<table>
<thead>
<tr>
<th>Test</th>
<th>Recommendation</th>
<th>QOE</th>
<th>SOR</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>
<tr>
<td>MammaPrint</td>
<td>Clinician may use the 70-gene assay to guide decisions on adjuvant systemic therapy</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>Prosigna</td>
<td>Clinician may use the PAM50 risk of recurrence score, in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td><strong>Node-positive (1-3 nodes)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MammaPrint</td>
<td>Clinician may use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization</td>
<td>High</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

HER2: human epidermal growth factor receptor 2; QOE: quality of evidence; SOR: strength of recommendation.
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.81 Table 3 summarizes guidelines on the use of biomarkers in patients with invasive breast cancer.

Table 3. 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><strong>Oncotype DX</strong></td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>in patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MammaPrint</strong></td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy</td>
<td>1A</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prosigna</strong></td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EndoPredict</strong></td>
<td>For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy</td>
<td>1B</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>to patients with ER-positive/HER2-negative, lymph node-negative and lymph node-positive (1 to 3 nodes) disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breast Cancer Index</strong></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.
FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer

In 2017, an international expert Panel, including members from the United States, convened for the 15th St. Gallen International Breast Cancer Conference. The Panel reviewed current evidence on locoregional and systemic therapies for early breast cancer. Table 4 summarizes relevant recommendations.

<table>
<thead>
<tr>
<th>Table 4. Therapies by Breast Cancer Diagnosis</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Group</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy for patients with node-negative breast cancer</td>
<td>The Panel endorsed the following gene expression assays for guiding the decision on adjuvant chemotherapy in node-negative cancers: 21-gene recurrence score, the 70-gene signature, the PAM50 ROR score, the EPclin score, and the Breast Cancer Index.82,</td>
</tr>
<tr>
<td>Adjuvant chemotherapy for patients with node-positive breast cancer</td>
<td>“The Panel did not uniformly endorse the use of gene expression signatures for making treatment decisions regarding adjuvant chemotherapy in node-positive cases.”82,</td>
</tr>
<tr>
<td>Extended endocrine therapy for patients recurrence free at 5 years</td>
<td>“The Panel did not recommend the use of gene expression signatures for choosing whether to recommend extended adjuvant endocrine treatment, as no prospective data exist and the retrospective data were not considered sufficient to justify the routine use of genomic assays in this setting.”82,</td>
</tr>
</tbody>
</table>

U.S. Preventive Services Task Force Recommendations

Not applicable.

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.83, 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+ estrogen receptor, 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)
REFERENCES


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


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FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer


POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2011</td>
<td>New Policy</td>
<td>Policy updated with literature search; rationale revised, references updated, no change in policy statement.</td>
</tr>
<tr>
<td>December 2012</td>
<td>Policy Update</td>
<td>Policy updated with literature search; several new references added. Policy statement revised to include addition of bilateral disease as investigational, use of Oncotype testing is investigational for women with DCIS, revise MammaPrint to be not medically necessary and add NexCourse Breast IHC4 as investigational.</td>
</tr>
<tr>
<td>June 2013</td>
<td>Policy Update</td>
<td>Policy updated with literature review. References 2, 15-16, 26-33, 37, 39, 43, 44, 47-50, 53-55, 62-67, 74, 76, 77 85-88, 90, 92-98, 102-105, 108-109, 117, 121-122, and 126 added references 1, 12, 106 and updated. 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 not medically necessary.</td>
</tr>
<tr>
<td>September 2015</td>
<td>Policy Update</td>
<td>Policy updated with literature review through October 10, 2016. Reorganized by indication rather than test. References 7, 11, 14-16, 31, and 43 added; several references removed. Policy statement added that Breast Cancer Index, EndoPredict and Prosigna are medically necessary for same indication as Oncotype. Other statements revised to reflect these tests investigational for other indications.</td>
</tr>
</tbody>
</table>
# FEP 2.04.36 Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

<table>
<thead>
<tr>
<th>Date</th>
<th>Policy Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2017</td>
<td>Policy updated with literature review through March 21, 2017 for indications 6-9 and 11-14 only. References 1, 6, 8-12, 18-24, 37-42, and 45-50 were added. Policy statements unchanged.</td>
</tr>
<tr>
<td>March 2018</td>
<td>Policy updated with literature review through September 11, 2017; references 34, 41, 45, 53, and 55-57 were added. Policy statements unchanged.</td>
</tr>
<tr>
<td>March 2019</td>
<td>Policy updated with literature review through September 4, 2018; references 16, 17, 19-21, 23, 24, 37, 38, 55, 59, and 82 were added. Policy statement was changed for indications pertaining to adjuvant chemotherapy. MammaPrint was added to the list of tests which are considered &quot;medically necessary&quot;.</td>
</tr>
</tbody>
</table>

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