FEP Medical Policy Manual

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

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Related Policies:

None

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

Description

Description

Laboratory tests have been developed to detect the expression, via messenger RNA, of different genes in breast tumor tissue and combine the results to determine prognosis in patients with 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 triple-negative (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2) breast cancer (TNBC), or to recommend extended endocrine therapy in patients who are recurrence-free at 5 years. This report summarizes the evidence for 6 tests and is organized by indication.

OBJECTIVE

The objective of this evidence review is to determine whether Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, Prosigna, and Insight TNBCtype 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 (ie, 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 (eg, tamoxifen, aromatase inhibitors);
- when the test result aids the patient in deciding on chemotherapy (ie, 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.

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.

The use of the MammaPrint assay 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 (ie, estrogen receptor-positive or progesterone receptor-positive);
- human epidermal growth factor receptor 2-negative;
- stage T1 or T2 or operable T3 at high clinical risk (see Policy Guidelines);
- one to 3 positive nodes;
- who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors);
- when the test result aids the patient in deciding on chemotherapy (ie, 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 Oncotype DX, EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna assays 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 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.

All other indications for the 21-gene RT-PCR assay (ie, 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 (ie, 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**.

The use of Insight TNBCtype to aid in making decisions regarding chemotherapy in women with triple-negative breast cancer is considered **investigational.**

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

POLICY GUIDELINES

In the MINDACT trial (Cardoso 2016), low versus high clinical risk was determined using the Adjuvant! Online tool (version 8.0 with HER2 status, www.adjuvantonline.com). The Adjuvant tool includes factors for age, comorbidities, ER status, tumor grade and size and number of positive nodes. In MINDACT, ER-positive, HER2-negative, node-positive patients were classified as high clinical risk if they met any of the following additional criteria:

- Grade: well differentiated; tumor size 2.1 to 5 cm
- Grade: moderately differentiated; tumor size, any size
- Grade: poorly differentiated or undifferentiated; tumor size, any size

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.

Unfavorable features that may prompt testing in tumors from 0.6 cm 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.

Assays of genetic expression in tumor tissue are complex test procedures; each test will likely be available at 1 or a limited number of reference laboratories.

FDA REGULATORY STATUS

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 (FDA) 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 Index^{SM} (Biotheranostics), EndoPredict (distributed by Myriad), and Insight TNBCtype (Insight Genetics) are not FDA-approved.

RATIONALE

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 human epidermal growth factor receptor 2 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% confidence interval [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.

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 the patients in these studies were classified as 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 a 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% 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 and a randomized controlled trial providing evidence for clinical utility. 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%). The randomized controlled trial Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy 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 (1 to 3 Nodes) Invasive Breast Cancer

For decisions on the management of early-stage node-positive disease, Oncotype DX, EndoPredict, MammaPrint, and Prosigna were evaluated. Only studies presenting a minimum of 5 year distant recurrence rates or 5 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 3 prospective-retrospective studies. The prospective-retrospective studies showed that Oncotype DX stratifies node-positive patients into high- and low-risk for distant recurrence-free survival. The studies have proposed different cutoffs for low-risk. One of the studies with a recurrence score cutoff for low-risk of 18 reported CIs for estimates and those are very wide. The analysis from the Plan B 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 (recurrence score <=11) experienced higher rates of survival than patients classified as high-risk, though no rates were provided. Five-year DFS in patients with 1-3 positive nodes or pN1 disease and recurrence score <=11 treated with endocrine therapy alone (n=110) was 94.4% (95% CI, 89.5 to 99.3%). There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy but consensus on cutoffs and 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 EndoPredict score patients was estimated to be 5% (95% CI, 1% to 9%). In the other study, the 10-year distant recurrence rate in low-risk EndoPredict 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 the 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. The randomized controlled trial Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy showed 5-year distance recurrence rates below the 10% threshold among node-positive (1 to 3 nodes) 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-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the Prosigna risk of recurrence (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 the 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, 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 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 with EndoPredict. However, in 1 of the analyses, the lower-bound of the 95% CI for the distant recurrence rate in the high-risk group falls within a range that may be clinically meaningful for decision-making about avoiding extended endocrine treatment both at 5-10 years (5.9%; 95% CI, 2.2% to 9.5%) and at 5-15 years (15.1%; 95% CI, 4.0% to 24.9%). The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported although 1 publication reported that EPclin was prognostic after controlling for a clinical prediction tool. Additional prospective trials or retrospective-prospective studies of archived samples are needed to confirm risk of disease recurrence with sufficient precision in both low- and high-risk groups. 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 Breast Cancer Index, the evidence includes 3 analyses of archived tissue samples from 2 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.

Triple-Negative Breast Cancer

The Insight TNBCtype Test is the only assay investigated for patients with TNBC.

Insight TNBCtype Test

For individuals who have TNBC considering neoadjuvant chemotherapy who receive gene expression profiling with the Insight TNBCtype test, the evidence includes retrospective cohort studies. Although the studies have shown that TNBC subtypes may differ in their response to neoadjuvant chemotherapy, as the studies were not prospectively designed or powered to specifically address the TNBC population or their specific therapeutic questions, conclusions cannot be drawn based on these findings. Additional Simon et al (2009) category A or B studies are required. Additionally, further clarity about how the test would inform clinical practice is still 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

Adjuvant Chemotherapy for Node-Negative Breast Cancer

Current guidelines from the NCCN for breast cancer (v.6.2020)[2,] provide a summary table assessing multigene assays to inform the addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy (page BINV-N). 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 algorithm:

- "Strongly consider 21-gene RT-PCR assay" for node-negative, ER+ [estrogen receptor-positive], HER2- [human epidermal growth factor receptor 2-negative] breast cancer with "pT1, pT2, or pT3; and pN0" and tumor greater 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.6.2020)[2] 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 MammaPrint for this population is 1 and the level of evidence and consensus for Oncotype DX and EndoPredict for this population is 2A. In addition to the summary table, the following recommendation appears in an updated algorithm:

- "Consider gene expression 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 gene expression assays in women with 4 or more ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for these groups should be based on clinical factors." For N1mi and N1, "gene expression 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."

Extended Endocrine Therapy

The latest NCCN guideline (v.6.2020) provides a flow chart on adjuvant endocrine therapy (aromatase inhibitors [AI] or tamoxifen) recommendations and considerations, based on menopausal status at diagnosis and after 5 years of therapy, and on prior therapy history (page BINV-K).[2] The following Table 1 summarizes the contents of the flow chart:

Table 1. NCCN Recommendations and Considerations for Extended Endocrine Therapy

Menopausal Status at Diagnosis	Therapy History	Current Menopausal Status	Recommendations or Considerations
Premenopausal	• Tamoxifen 5 years (category 1) • AI 5 years (category 1)	Postmenopausal	• Recommend AI 5 more years (category 1) • Consider tamoxifen 5 more years
Premenopausal	• Tamoxifen 5 years (category 1) • AI 5 years (category 1)	Premenopausal	• Consider tamoxifen 5 years • No further endocrine therapy
Postmenopausal	AI 5 years (category 1)	Postmenopausal	Consider AI for an additional 3-5 more years
Postmenopausal	AI 2 to 3 years (category 1)	Postmenopausal	Recommend tamoxifen to complete 5 years (category 1)

Postmenopausal	Tamoxifen 2 to 3 years	Postmenopausal	• Recommend AI to complete 5 years (category 1) • Recommend up to 5 years of AI (category 2B)
Postmenopausal	Tamoxifen 4.5 to 6 years	Postmenopausal	• Recommend AI 5 more years (category 1) • Consider tamoxifen to complete 10 years
Postmenopausal	No AI therapy (contraindicated or declined)	Postmenopausal	• Recommend tamoxifen 5 years (category 1) • Consider tamoxifen up to 10 years

AI: aromatase inhibitor; NCCN: National Comprehensive Cancer Network.

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO) (2017) 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.[84,] and published a focused update of those guidelines in 2019[85,]. The ASCO also updated endorsement of the Cancer Care Ontario recommendations on the Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer in 2019. The recommendations are consistent with the table below.[86,] Table 28 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 and Triple-Negative Breast Cancer

Test	Recommendation	QOE	SOR
Node-negative			
Oncotype DX	"For patients older than 50 years and whose tumors have Oncotype DX recurrence scores of less than 26, and for patients age 50 years or younger whose tumors have Oncotype DX recurrence scores of less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone."	High	Strong
	"For patients age 50 years or younger with Oncotype DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy"	Intermediate	Moderate
	"Patients with Oncotype DX recurrence scores of greater than 30 should be considered candidates for chemoendocrine therapy"	High	Strong
	"..oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30"	Insufficient	Moderate
EndoPredict	Clinician may use the 12-gene risk score to guide decisions on adjuvant systemic chemotherapy	Intermediate	Moderate

Breast Cancer Index	Clinician may use the Breast Cancer Index to guide decisions on adjuvant systemic therapy	Intermediate	Moderate
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
Triple-negative breast cancer			
EndoPredict	If a patient has triple-negative breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions for adjuvant systemic therapy.	Insufficient	Strong
Breast Cancer Index	If a patient has triple-negative breast cancer, the clinician should not use the Breast Cancer Index to guide decisions about adjuvant systemic therapy.	Insufficient	Strong
Oncotype DX	If a patient has triple-negative breast cancer, the clinician should not use the 21-gene RS (Oncotype DX) to guide decisions for adjuvant systemic therapy.	Insufficient	Strong

HER2: human epidermal growth factor receptor 2; QOE: quality of evidence; SOR: strength of recommendation.

ASCO also has guidelines on adjuvant endocrine therapy. In 2018, ASCO updated its guidelines from 2014[3,4] on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer.[87] The update included a qualifying statement that none of the studies used to develop the recommendations showed improvements in overall survival (OS) with extended therapy, and that the recommendations are based on benefits that include prevention of distant recurrence and prevention of second breast cancers. Therefore, the decision to receive extended therapy should involve the weighing of recurrence risk against potential therapy risks and side effects. Recommendations based on nodal status are as follows:

- "Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine therapy based on considerations of recurrence risk using established prognostic factors. However, as recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.
- Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine therapy."

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

In 2017, an international expert Panel, including members from the U.S., 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 3 summarizes relevant recommendations.

Table 3. Therapies by Breast Cancer Diagnosis

Breast Cancer Group	Recommendation

Adjuvant chemotherapy for patients with node-negative breast cancer	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.[88]
Adjuvant chemotherapy for patients with node-positive breast cancer	"The Panel did not uniformly endorse the use of gene expression signatures for making treatment decisions regarding adjuvant chemotherapy in node-positive cases."[88]
Extended endocrine therapy for patients recurrence-free at 5 years	"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."[88]

In 2019, the 16th St. Gallen International Breast Cancer Conference again reviewed current evidence on locoregional and systemic therapies for early breast cancer.[89] Statements related to use of genomic assays included the following:

- "The Panel believed strongly that genomic assays are valuable for determining whether or not to recommend adjuvant chemotherapy in T1/T2 N0 ER-positive breast cancers, and recognized the value of such tests in patients with ER-positive tumors and limited nodal involvement."
- "The Panel strongly endorsed the value of genomic assays for determining whether to recommend chemotherapy in T1/T2 N0 tumors, T3 N0 tumors, and TxN1 (1 to 3 positive LN)."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
December 2012	Replace policy	Policy updated with literature search; rationale revised, references updated, no change in policy statement.
June 2013	Replace policy	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.

Date	Action	Description
September 2015	Replace policy	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.
March 2017	Replace policy	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.
December 2017	Replace policy	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.
March 2018	Replace policy	Policy updated with literature review through September 11, 2017; references 34, 41, 45, 53, and 55-57 were added. Policy statements unchanged.
March 2019	Replace policy	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 "medically necessary”.
March 2020	Replace policy	Policy updated with literature review through September 16, 2019; references added. Medically necessary statement for MammaPrint added for node-positive (1 to 3 nodes) women making decisions regarding adjuvant chemotherapy.

Date	Action	Description
March 2021	Replace policy	Policy updated with literature review through September 21, 2020; references added. New indication added for individuals with triple-negative (estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2) breast cancer, considering neoadjuvant chemotherapy, who receive gene expression profiling with Insight TNBCtype. Investigational policy statement was added for this new indication. No other changes to policy statements.