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# 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

### Annual Effective Policy Date: April 1, 2026

### Original Policy Date: December 2011

### 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 or triple-negative breast cancer (TNBC) (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2) , 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), EndoPredict, the Breast Cancer Index, MammaPrint, or Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered **medically necessary** in women with primary, invasive, node-negative breast cancer meeting all of the following characteristics:

- unilateral tumor (see Policy Guidelines);
- 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.

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, node positive 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);
- 1 to 3 positive nodes (N1);
- no distant metastases;
- who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors);
- eligible for a chemotherapy regimen containing a taxane, an anthracycline, or both;
- 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 use of Oncotype Dx to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered **medically necessary** in women with primary, invasive, node positive breast cancer meeting all of the following characteristics:

- postmenopausal (defined as previous bilateral oophorectomy or more than 12 months since the last menstrual period and no previous hysterectomy);
- 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);
- 1 to 3 positive nodes (N1);
- no distant metastases;
- who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors);

- eligible for a chemotherapy regimen containing a taxane, an anthracycline, or both;
- 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 use of Oncotype Dx to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in premenopausal women (defined as le ss than 6 months since the last menstrual period) with primary, invasive, node positive breast cancer is considered **investigational** (see Policy Guidelines).

The use of EndoPredict, the Breast Cancer Index, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in individuals with primary, invasive, node positive breast cancer is considered **investigational**.

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 (see Policy Guidelines).

All other indications for the 21-gene RT-PCR assay (ie, Oncotype DX), EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna, including to consider the length of treatment with endocrine therapy, repeat testing with same test, or combination testing with various tests, 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**.

Use of the DCISion RT assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ 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

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 [202 3]) have defined positive, negative, and equivocal *HER2* test results.

## Unilateral Bilateral Premenopausal

Most breast cancer is unilateral, occurring in one breast. Bilateral breast cancer, breast cancer in both breasts, can be synchronous or metachronous. Synchronous is generally defined as occurring within 6 months, but other intervals are used (3 months or even 12 months), and overall, inconsistency in the use of the term "bilateral breast cancer" occurs. It is difficult to clearly know if a second breast cancer appearing within months of the first is metastatic spread or a new primary. There are no professional guidelines on use of gene expression assays in bilateral breast cancers, although small studies show Oncotype Dx score discordancy in synchronous bilateral ER-positive HER2-negative breast cancer with associated chemotherapy recommendation changes of 50% to 57%. No health outcomes were reported from the change in chemotherapy recommendations. As such, the

position relates only to unilateral breast cancer although at the local level consideration could be given to genetic expression assay in a second cancer in the contralateral breast.

## Premenopausal

The position on premenopausal women with node positive breast cancer differs from the NCCN guidelines (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). The NCCN guidelines have a 2A recommendation for OncotypeDx testing of premenopausal women with 1-3 positive lymph nodes based on the RxPONDER trial (Kalinsky et. al., 2021; PMID 34914339). Based on this test, the NCCN guidelines have a recommendation to "consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an Aromatase inhibitor." Note that RxPONDER was not designed to test whether chemotherapy can be replaced by ovarian suppression, and that among premenopausal women, invasive disease - free survival at 5 years was 89.0% with endocrine-only therapy and 93.9% with chemoendocrine therapy (hazard ratio, 0.60; 95% CI, 0.43 to 0.83; P = 0.002), with a similar increase in distant relapse - free survival (hazard ratio, 0.58; 95% CI, 0.39 to 0.87; P = 0.009) indicating benefit of chemoendocrine therapy. While the evidence then is insufficient to support Oncotype DX testing as perhaps all premenopausal women benefit from chemoendocrine therapy regardless of Oncotype DX recurrence score, with the NCCN 2A recommendation for using Oncotype Dx testing for premenopausal women a local decision might need to be made.

## Clinical Risk

In the MINDACT trial (Cardoso et. al., 2016; PMID: 27557300), 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 cm to 5 cm
- Grade: moderately differentiated; tumor size, any size
- Grade: poorly differentiated or undifferentiated; tumor size, any size

## Multiple Ipsilateral Tumors

Gene expression assay testing on multiple ipsilateral primary tumors could start with assessing the most histologically aggressive, as concordance of Oncotype Dx score with Nottingham score is strong. However, a low Oncotype Dx score indicating no need for adjuvant chemotherapy from the most aggressive appearing tumor might not negate the need for Oncotype Dx testing of other primary tumors. The literature base for this strategy is slim; but, for ipsilateral multiple tumors, Toole, et al. show that 22% (4 out of 18) had Oncotype Dx score differences that led to changes in management. Additionally though, Toole, et al. found that in a small number of cases the histology and grade were the same on ipsilateral lesions yet had significantly different Oncotype Dx scores altering chemotherapy recommendations. Larger, prospective studies are needed including clinical outcomes from management changes. Consideration at the local level could be given to histologically distinct tumors meeting the other criteria for gene expression assay testing, or serial testing. There is no literature assessing the use of one gene expression assay on one tumor and a different gene expression assay on another ipsilateral tumor.

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 [2023]) have defined positive, negative, and equivocal *HER2* test results.

## Male Breast Cancer

For the purposes of this evidence review, the terms males and females are used to denote sex assigned at birth. Due to the limited participation of males in breast cancer clinical trials, the recommendations for managing breast cancer in males are predominantly based on extrapolations from data obtained from female breast cancer trials. While there are some biological and clinical differences between breast cancer in males and females, the management of breast cancer in males generally mirrors that of females, with specific considerations for male patients. According to the current NCCN guidelines on breast cancer, there is a scarcity of data on the use of molecular assays for predicting prognosis and chemotherapy benefits in male

breast cancer patients. Nonetheless, the NCCN highlights that existing data indicate the 21-gene assay recurrence score (Oncotype DX) offers valuable prognostic insights for males with breast cancer.(https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf).

# BENEFIT APPLICATION

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

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.

# FDA REGULATORY STATUS

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.

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 (Biotheranostics), EndoPredict (distributed by Myriad), Insight TNBCtype (Insight Genetics), and DCISionRT (PreludeDX) are not FDA cleared or 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 an 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 an 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 an 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%-96%), but not as high survival for the low-risk group not treated with tamoxifen (83%, 95% CI, 76%-88%). The randomized controlled trial (Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy, 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 an improvement in the net health outcome.

### BluePrint (80-gene expression assay)

For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with BluePrint (80-gene expression assay) in conjunction with MammaPrint or alone, the evidence includes a few observational studies with no direct evidence that BluePrint improves the net health outcome. 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 evidence is insufficient to determine that the technology results in an 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 an 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 a clinical utility study demonstrating that postmenopausal women with a RS score of 0 to 25 could safely forego adjuvant chemotherapy without compromising invasive disease - free survival or distant relapse - free survival. In the RxPONDER trial, participants (N =5083) with hormone-receptor - positive, HER2-negative breast cancer, 1 to 3 positive axillary lymph nodes, and a RS of 25 or lower were randomized to endocrine therapy only or to chemotherapy plus endocrine (chemoendocrine) therapy. Among postmenopausal

women (66.8%), estimates of invasive disease - free survival at 5 years were 91.3% in the chemoendocrine group and 91.9% in the endocrine-only group (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 1.02; 95% CI, 0.82 to 1.26; P =.89). In premenopausal women, the rate of invasive disease - free survival at 5 years among those in the chemoendocrine group was 93.9%, as compared with 89.0% among those in the endocrine-only group (absolute difference, 4.9 percentage points), with a significant chemotherapy benefit (hazard ratio for invasive disease recurrence, new primary cancer [breast cancer or another type], or death, 0.60; 95% CI, 0.43 to 0.83; P =.002). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

### 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 that the technology results in an improvement in the net health outcome.

### 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 an 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 that the technology results in an improvement in the net health outcome.

## Ductal Carcinoma In Situ

### 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 that the technology results in an improvement in the net health outcome.

### DCISionRT

For individuals who have DCIS considering radiotherapy who receive gene expression profiling with DCISionRT, the evidence includes retrospective validation studies. One Simon et al (2009) category B study provided evidence for clinical validity which showed no benefit of radiation therapy among a group of participants classified as low risk using the DCIS RT score at a threshold of <3 (absolute risk difference for invasive recurrence 1.2% (-5.7% to 8.2%). However, it is unclear whether the estimated 10-year recurrence risk for this group (12.4%; 95% CI 7.2% to 20.8% for invasive recurrence) is low enough to consider changing management or is estimated with sufficient precision. Conclusions are also limited because there are no comparison recurrence estimates for women based on the standard of care (risk predictions based on clinical algorithms).The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

## 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 that the technology results in an improvement in the net health outcome.

### 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 to 10 years (5.9%; 95% CI, 2.2% to 9.5%) and at 5 to 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 one 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 that the technology results in an improvement in the net health outcome.

### 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 that the technology results in an improvement in the net health outcome.

For individuals who have early-stage node-positive (1 to 5 nodes) invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with the Breast Cancer Index, the evidence includes 4 analyses of archived tissue samples from previously conducted clinical trials. The analyses showed low distant recurrence rates and high distant recurrence-free survival rates in patients classified as low-risk with the test. The 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 that the technology results in an improvement in the net health outcome.

### 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 that the technology results in an improvement in the net health outcome.

### 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 that the technology results in an improvement in the net health outcome.

## 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 that the technology results in an improvement in the net health outcome.

## Repeat Testing

For individuals with breast cancer who receive multiple (repeat) assays of genetic expression in tumor tissue to determine prognosis for a single decision, the evidence includes studies comparing different tests in groups of individuals but no direct evidence evaluating repeat testing with the same test or a combination of tests performed on the same individual. Additionally, clinical practice guidelines recommend against a strategy of repeat testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## Male Breast Cancer

For individuals with male breast cancer who receive gene expression profiling with Oncotype DX (21-gene signature), the evidence includes 1 systematic review and meta-analysis of retrospective cohort studies, focused on Oncotype DX in both female and male patients with ER-positive, HER2-negative early breast cancer. Only 1% of the patients had male breast cancer. The likelihood of male patients having 21-gene assay scores was comparable to that of female patients. Drawing meaningful conclusions regarding Oncotype DX scores is challenging given the inherent study limitations such as ascertainment, confounding, and selection biases. No studies were identified evaluating the EndoPredict, Breast Cancer Index, MammaPrint/BluePrint, or Prosigna tests in male breast cancer patients. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

# SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### American Society of Clinical Oncology

In June 2022, the American Society of Clinical Oncology (ASCO) published updated clinical practice guidelines on the use of breast cancer biomarker assay results to guide adjuvant endocrine and chemotherapy decisions in early-stage breast cancer. The recommendations related to the interventions and populations included in this evidence opinion are listed in Table 1.[97,]

The guidelines do not address the use of assays such as Oncotype DCIS or DCISionRT to guide decisions about radiation therapy in individuals with DCIS.

**Table 1. American Society of Clinical Oncology Guidelines on the Use of Biomarker Assays to Guide Adjuvant Endocrine and Chemotherapy Decisions in Early-Stage Breast Cancer- 2022**

| Interventions | Recommendation | Evidence Quality | Strength of Recommendation |
|---|---|---|---|
| ***Newly Diagnosed ER-Positive, HER2-Negative Breast Cancer*** | | | |
| Oncotype DX (21-generecurrence score, 21-gene RS) | 1.1. If a patient has node-negative breast cancer, the clinician may use Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy | High | Strong |
| | 1.2. In the group of patients in Recommendation 1.1 with Oncotype DX score greater than or equal to 26, the clinician should offer chemoendocrine therapy | High | Strong |
| | 1.3. In the group of patients in Recommendation 1.1 who are 50 years of age or younger with Oncotype DX score 16 to 25, the clinician may offer chemoendocrine therapy | Intermediate | Moderate |
| | 1.4. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the clinician may use Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy | High | Strong |
| | 1.5. In the group of patients in Recommendation 1.4, the clinician should offer chemoendocrine therapy for those whose Oncotype DX score is greater than or equal to 26 | High | Strong |
| | 1.6. If a patient is premenopausal and has node-positive breast cancer with 1-3 positive nodes, Oncotype DX test should not be offered to guide decisions for adjuvant systemic chemotherapy | High | Moderate |
| | *Qualifying statement:*The genomic assay is prognostic and may be used for shared patient-physician treatment decision making | | |
| | 1.7. If a patient has node-positive breast cancer with more than 3 positive nodes, the evidence on the clinical utility of routine Oncotype DX test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use | Insufficient | Moderate |
| MammaPrint (70-genesignature) | 1.8. If a patient is older than 50 and has high clinical risk breast cancer, that is node-negative or node-positive with 1-3 positive nodes, the clinician may use MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy | Intermediate | Strong |
| | 1.9. If a patient is 50 years of age or younger and has high clinical risk, node negative or node-positive with 1-3 positive nodes breast cancer, the clinician should not use the MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy | High | Strong |
| | 1.10. If a patient has low clinical risk, regardless of age, the evidence on clinical utility of routine MammaPrint test is insufficient to recommend its use | Intermediate | Moderate |
| | 1.11. If a patient has node-positive breast cancer with more than 3 positive nodes, the evidence on the clinical utility of routine MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use | Insufficient | Strong |
| | *Qualifying statement:*The genomic assay is prognostic and may be used for shared patient-physician treatment decision making | | |
| EndoPredict (12-generisk score) | 1.12. If a patient is postmenopausal and has breast cancer that is node negative or node-positive with 1-3 positive nodes, the clinician may use EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy | Intermediate | Moderate |

| | | | |
|---|---|---|---|
| | 1.13. If a patient is premenopausal and has breast cancer that is node negative or node-positive with 1-3 positive nodes, the clinician should not use EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy | Insufficient | Moderate |
| | 1.14. If a patient has breast cancer with more than 3 positive nodes, evidence on the clinical utility of routine use of EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy is insufficient | Intermediate | Moderate |
| Prosigna (PAM50) | 1.15. If a patient is postmenopausal and has breast cancer that is node negative, the clinician may use the Prosigna test to guide decisions for adjuvant systemic chemotherapy | Intermediate | Moderate |
| | 1.16. If a patient is premenopausal, and has node-negative or node-positive breast cancer the clinician should not use the Prosigna test to guide decisions for adjuvant systemic chemotherapy | Insufficient | Moderate |
| | 1.17. If a patient is postmenopausal and has node-positive breast cancer with 1-3 positive nodes, the evidence is inconclusive to recommend the use of Prosigna test to guide decisions for adjuvant endocrine and chemotherapy | Intermediate | Moderate |
| | 1.18. If a patient has node-positive breast cancer with more than 3 positive nodes, evidence on the clinical utility of routine use of Prosigna test to guide decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use | Insufficient | Strong |
| ***Extended Endocrine Therapy for ER Receptor-Positive HER2-Negative Breast Cancer*** | | | |
| Oncotype DX,EndoPredict, Prosigna | 1.23. If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4 tests to guide decisions about extended endocrine therapy | Intermediate | Moderate |
| Breast Cancer Index(BCI) | 1.24. If a patient has node-negative or node-positive with 1-3 positive nodes breast cancer and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI or a sequence of tamoxifen followed by AI | Intermediate | Moderate |
| | 1.25. If a patient has node-positive breast cancer with more than 3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI or asequence of tamoxifen followed by AI | Intermediate | Strong |
| Clinical treatment score post-5 years (CTS5) | 1.26. If a patient is postmenopausal and had invasive breast cancer and is recurrence-free after 5 years of adjuvant endocrine therapy, the clinical treatment score post-5 years (CTS5) web tool may be used to calculate the estimated risk of late recurrence (recurrence between years 5-10), which could assist in decisions about extended endocrine therapy | Intermediate | Moderate |
| ***HER2-Positive Breast Cancer or Triple-Negative Breast Cancer*** | | | |
| Oncotype DX,EndoPredict, MammaPrint, BCI,Prosigna, | 1.27. If a patient has HER2-positive breast cancer or TNBC, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy | Insufficient | Strong |

Source: adapted from Andre et al (2022) Summary of Recommendations Table (Data Supplement)[97,]

## Breast Cancer Therapy Expert Group

In 2020, the Breast Cancer Therapy Expert Group (BCTEG) published guidance on the use of genomic testing in early breast cancer. [95,] The guidance was intended for community oncologists and included the following clinical practice points:

- "Genomic testing is generally only indicated in patients with hormone receptor-positive and HER2 negative tumors, and those with up to 3 positive nodes.
- Genomic testing should generally not be performed for patients with hormone receptor negative disease, > 3 positive nodes, HER2 positivity, or TNBC outside the context of a clinical trial.
- Genomic testing should generally not be performed in patients for whom the results of the testing will not affect the course of treatment.
- Discordance between available genomic tests is expected because the different tests were developed and validated across a range of patient populations and treatment backgrounds; performing more than one genomic test on a patient should be avoided, as uncertainties in risk assignment may result."

## National Comprehensive Cancer Network

The current NCCN guidelines for breast cancer are Version 5. 2024.[4,] Guidelines are updated frequently; refer to the source for most recent guidelines. Recommendations related to the interventions and populations included in this evidence opinion, current as of , 2024 , are listed in Table 2.

The guidelines state, "Since results of different assays may not be concordant with each other and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor."

The guidelines do not address the use of assays such as Oncotype DCIS or DCISionRT to guide decisions about radiation therapy in individuals with DCIS.

### Table 2. National Comprehensive Cancer Network Recommendations on the Use of Biomarker Assays to Guide Adjuvant Systemic Therapy[a,b] Decisions in Early-Stage Breast Cancer

| Assay | Predictive | Prognostic | NCCN Category of Preference | NCCN Category of Evidence and Consensus |
|---|---|---|---|---|
| 21-gene (Oncotype Dx) (for pN0) | Yes | Yes | Preferred | 1 |
| 21-gene (Oncotype Dx) for pN1 (1-3 positive nodes)[c] | Yes | Yes | Postmenopausal: Preferred | 1 |
| | | | Premenopausal: Other | 2A |
| 70-gene (MammaPrint) for pN0 and pN1 (1-3 positive nodes) | Not determined | Yes | Other | 1 |
| 50-gene (Prosigna) for pN0 and pN1 (1-3 positive nodes) | Not determined | Yes | Other | 2A |
| 12-gene (EndoPredict) for pN0 and pN1 (1-3 positive nodes) | Not determined | Yes | Other | 2A |
| Breast Cancer Index (BCI) | Predictive of benefit of extended adjuvant endocrine therapy | Yes | Other | 2A |

Source: [National Comprehensive Cancer Network]

a- Gene expression assays provide prognostic and therapy-predictive information that complements T, N, M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
b- See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth)
c- In the overall study population of the Tx PONDER trial, 10.3% had high-grade disease and 9.2% had 3 involved nodes.

## 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€š, BluePrint and TargetPrint as investigational. Policy statement on PAM50 updated to Prosigna€š. 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. |
| 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. |
| March 2022 | Replace policy | Policy updated with literature review through September 29, 2021; references added. New indication added for the Breast Cancer Index for node-positive (1 to 3 nodes) individuals making decisions regarding extended endocrine therapy; evidence is insufficient. In the first investigational policy statement, revised "extended tamoxifen treatment" to "extended endocrine therapy". Policy statements otherwise unchanged. |
| March 2023 | Replace policy | Policy updated with literature review through September 13, 2022; references added. New indications and investigational policy statements added for DCISion RT assay in DCIS and for multiple (repeat) performed in the same individual. New medically necessary policy statement with criteria added for Oncotype DX in node positive breast cancer. Pruned evidence opinion for clarity and to remove outdated references. |
| March 2024 | Replace policy | Policy updated with literature review through September 26, 2023; references added. Policy statements unchanged. |
| March 2025 | Replace policy | Policy updated with literature review through October 18, 2024; references added. New indications and evidence reviews added for the BluePrint and Male Breast Cancer. Policy statements unchanged. |
| March 2026 | Replace policy | Policy updated with literature review through October 18, 2024; references added. New indications and evidence reviews added for the BluePrint and Male Breast Cancer. Policy statements unchanged. |