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

**Policy #** 00211
Original Effective Date: 03/01/2007
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*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

## When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®‡), EndoPredict®‡, the Breast Cancer Index (BCI)SM‡, Prosigna®‡ and MammaPrint®‡ assay to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy in women with primary, invasive breast cancer to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®‡), EndoPredict®‡, the Breast Cancer Index (BCI)SM‡, Prosigna®‡ and MammaPrint®‡ assay to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy in women with primary, invasive breast cancer will be considered when **ALL** of the following criteria are met:

- Surgery has been performed and a full pathological evaluation of the specimen has been completed; **AND**
- Unilateral tumor, **AND**
- Hormone receptor positive (i.e., estrogen receptor-positive [ER+], progesterone receptor-positive [PR+], or both); **AND**
- Human epidermal growth factor receptor 2 (HER2)-negative; **AND**
- Tumor size greater than 0.5 cm (stage T1b-T3); **AND**

- Node negative (lymph nodes with micrometastases [less than or equal to 2 mm in size] are considered node negative for this policy statement) OR one to three positive lymph nodes (NI); **AND**
- No distant metastases; **AND**
- No other breast cancer gene expression profiling assay has been conducted for this tumor (this includes testing on any metastatic foci or on other sites when the tumor is multifocal); **AND**
- When the test result will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option); **AND**
- When ordered within 6 months following diagnosis, since the value of the test for making decisions regarding delayed chemotherapy is unknown.

Eligible for coverage 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 (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 histological characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

Only one assay of genetic expression per tumor tissue specimen per indication will be eligible for coverage.
Based on review of available data, the Company may consider the use of a subset of genes from the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ ([DCIS]; ie, Oncotype DX®‡ Breast DCIS Score) to inform treatment planning to be **eligible for coverage**.**

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Patient Selection Criteria

Coverage eligibility for the use of the Oncotype DX®‡ DCIS assay to inform treatment planning will be considered when **ALL** of the following criteria are met:

- Pathology (excisional or core biopsy) reveals DCIS of the breast (no pathological evidence of invasive disease); **AND**
- FFPE (formalin-fixed paraffin-embedded) tissue specimen has at least 0.5 mm of DCIS length; **AND**
- Patient is a candidate for and is considering breast conserving surgery alone or breast conserving surgery combined with adjuvant radiation therapy; **AND**
- Test result will be used to determine treatment choice between surgery alone vs surgery with radiation therapy; **AND**
- Patient has not received and is not planning on receiving a mastectomy; **AND**
- The test was not used before.

Based on review of available data, the Company may consider the use of the Breast Cancer Index (BCI)SM‡ assay predict risk of late distant recurrence (years 5-10) and benefit of extended adjuvant endocrine therapy in women with primary, invasive breast cancer to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use the Breast Cancer Index (BCI)SM‡ assay to predict risk of late distant recurrence (years 5-10) and benefit of extended adjuvant endocrine therapy in women with primary, invasive breast cancer will be considered when **ALL** of the following criteria are met:

- Unilateral tumor, hormone receptor positive, HER2-negative; **AND**
- Early-stage disease T1b-T3 with no more than 1-3 positive lymph nodes and no evidence of distant breast cancer metastasis; **AND**
- Has been treated with adjuvant endocrine therapy (tamoxifen or aromatase inhibitors) for at least 5 years, patient is a candidate for extended adjuvant endocrine therapy and the test will be used in decision making; **AND**
- The test was not used for this indication and individual before.

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# When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers all other indications for the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX®‡), EndoPredict®‡, the Breast Cancer Index (BCI)SM‡, MammaPrint®‡, and Prosigna®‡, including determination of recurrence risk in invasive breast cancer patients with more than three positive lymph nodes, patients with bilateral disease, distant metastases, repeat testing with same test, combination testing with various tests (except BCI for extended endocrine therapy decisions when BCI was not used before), or to consider extended adjuvant endocrine therapy in all other situations to be **investigational.***

Based on review of available data, the Company considers use of the Oncotype DX®‡ Breast DCIS Score in all other situations to be **investigational**.*

Based on review of available data, the Company considers the use of BluePrint®‡ in conjunction with MammaPrint®‡ or alone to be **investigational.***

Based on review of available data, the Company considers the use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (e.g., TargetPrint®‡) to be **investigational.***

Based on review of available data, the Company considers the use of Insight TNBCtype to aid in making decisions regarding chemotherapy in women with triple-negative breast cancer to be **investigational.***
Based on review of available data, the Company considers the use of gene expression assays in men with breast cancer to be **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 [2013]) 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 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 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 [2013]) have defined positive, negative, and equivocal *HER2* test results.

# Background/Overview

**Newly Diagnosed Breast Cancer**

Per the Centers for Disease Control, breast cancer is a disease in which cells in the breast grow out of control, and can be found in the lobules, ducts, and connective tissue. Breast cancer affects individuals of all races and ethnicities and sexes. New cases are highest among White women (130.3 per 100,000) followed by Black women (125.4 per 100,000). Rates of death from breast cancer, however, are highest among Black women (26.8 per 100,000) followed by White women (18.8 per 100,000).

The most common breast cancers are invasive ductal carcinoma and invasive lobular carcinoma. Less common types of breast cancer include Paget's disease, medullary, mucinous, and inflammatory. In ductal carcinoma in situ (DCIS), the cancer cells are only in the lining of the ducts and have not spread to other tissues; DCIS may lead to invasive breast cancer. Most breast cancer diagnoses are female breast cancer diagnosed at a localized stage (confined to the primary site), with less diagnoses being regional (spread beyond the primary site or to regional lymph nodes) or distant (spread to other organs or remote lymph nodes). The Nottingham score is a histological scoring system reflecting the grade of breast cancers. It is a total of scores based on microscopic determination of tubule formation, nuclear pleomorphism, and mitotic activity with each given a score of 1 to 3. Thus, the lowest Nottingham score is 3 and the highest is 9, with higher values thought to predict more aggressiveness. Nottingham score of 3-5 is assigned Grade I, 6-7 assigned Grade II, and 8-9 assigned Grade III.

Most women with newly diagnosed breast cancer in the U.S. present with the early-stage or locally advanced (ie, nonmetastatic) disease. However, almost a third of women who are disease-free after

initial local and regional treatment develop distant recurrences during follow-up. Current breast cancer treatment regimens involve systemic adjuvant chemotherapy, hormonal therapy, biologic therapy, or a combination, depending on patients' baseline levels of recurrence risk, hormonal markers, and risk tolerance.

Women whose tumors are positive for human epidermal growth factor receptor 2 (*HER2*) should receive adjuvant therapy with a *HER2*-directed therapy (trastuzumab with or without pertuzumab). Decision-making about adjuvant biologic therapy for women with *HER2*-positive cancer is not discussed here. This review focuses on 4 decision points:

1. ***The decision to pursue adjuvant chemotherapy following locoregional therapy, with or without neoadjuvant chemotherapy, based on the predicted risk of recurrence, for women who are hormone receptor-positive but HER2-negative.*** The use of adjuvant chemotherapy reduces the risk of breast cancer recurrence but carries risks of systemic toxicity. The risk:benefit ratio must be considered for each patient, with a higher likelihood of net health benefits for patients with a greater baseline predicted risk of recurrence. Some of the individual considerations are discussed below. *HER2* expression independently confers an unfavorable prognosis, but assessing the independent effects of *HER2* is complicated in the presence of targeted therapy; therefore, BCBSA focuses specifically on patients without *HER2* expression.
2. ***The decision to pursue extended adjuvant endocrine therapy from 5 to 10 years for women who are hormone receptor-positive but HER2-negative and who have survived without a recurrence for 5 years.*** For patients with hormone receptor-positive tumors, the use of adjuvant endocrine therapy (tamoxifen and/or an aromatase inhibitor [AI], with or without ovarian suppression) for 5 to 10 years after an initial diagnosis has support in clinical practice. Support for extended endocrine therapy beyond the initial 5 years is inconsistent across various guidelines. The guidelines from the National Comprehensive Cancer Network (v4.2023) include various recommendations and considerations, based on menopausal status at diagnosis and after 5 years of therapy, and on prior therapy history (see Supplemental Information section). The guidelines also note that the optimal duration of AIs is uncertain. The American Society for Clinical Oncology's updated guidelines (2018) vary based on recurrence risk and nodal status (see Supplemental Information section).
3. ***The decision to pursue adjuvant radiotherapy in women with ductal carcinoma in situ.*** Adjuvant radiotherapy reduces the risk of local recurrences but has not been shown to change

the risk of distant recurrence or mortality. There may be a group of patients for whom the reduction in risk for local recurrence may not be large enough to justify the risks of radiotherapy.

4. ***The decision to pursue neoadjuvant chemotherapy in women with Triple-Negative Breast Cancer (TNBC).*** In women with TNBC, pathological complete response has been found to be heterogenous in the neoadjuvant setting and has been associated with prolonged overall survival. For example, although TNBC tends to be more aggressive than other breast cancer types and confers a less favorable prognosis, previous research has suggested that the 20% to 40% of women with TNBC who achieve pathological complete response may achieve a similar long-term survival prognosis as patients with non-TNBC breast cancers. This heterogeneity suggests that there may be subtypes of women with TNBC that significantly differ in their likelihood of response to neoadjuvant chemotherapy and differ in their risk:benefit treatment considerations.

**Selection of Adjuvant Chemotherapy Based on Risk of Recurrence**

An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant cytotoxic chemotherapy. For example, for women with early-stage invasive breast cancer (ie, cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of patients' baseline prognosis. However, the absolute benefit of chemotherapy depends on the underlying or baseline risk of recurrence. Women with the best prognosis have tumors that are small, early-stage, estrogen receptor-positive, and lymph node-negative (Table 1 shows recurrence risk for estrogen receptor-positive cancers for patients followed in the International Breast Cancer Study Group). Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy. These women have an approximately 15%, 10-year risk of recurrence with tamoxifen alone, which means that approximately 85% of these patients could avoid the toxicity of adjuvant cytotoxic chemotherapy if they could be accurately identified. Conventional risk classifiers (eg, Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and the number of affected lymph nodes. Consensus guidelines for defining receptor status exist; however, no single classifier is considered a criterion standard. As a result, a substantial number of patients are treated with chemotherapy who

fail to benefit. Better predictors of recurrence risk could help women's decision-making, some of whom may prefer to avoid chemotherapy if assured their risk is low.

**Table 1. Effect of Nodal Involvement, Tumor Size, and Grade on Annual Recurrence Hazard in Estrogen Receptor-Positive Breast Cancers**

| **Nodes** | **Recurrence, Hazard [a] (SE),%** | | | | |
|---|---|---|---|---|---|
| | *Years* | | | | |
| | 0-5 | 5-10 | 10-15 | 15-20 | 20-25 |
| 0 | 5.8 (0.5) | 3.3 (0.4) | 2.0 (0.4) | 2.1 (0.4) | 1.1 (0.4) |
| 1 to 3 | 9.5 (0.6) | 5.8 (0.6) | 3.0 (0.5) | 3.5 (0.7) | 1.5 (0.6) |
| ≥4 | 17.2 (0.9) | 10.9 (1.2) | 5.9 (1.2) | 3.8 (1.2) | 1.3 (0.9) |
| Size | | | | | |
| ≤2 cm | 7.0 (0.4) | 4.8 (0.4) | 2.9 (0.4) | 2.7 (0.5) | 1.5 (0.5) |
| >2 cm | 12.9 (0.6) | 6.1 (0.6) | 2.9 (0.5) | 2.7 (0.5) | 1.1 (0.5) |
| Grade | | | | | |
| 1 | 5.8 (0.6) | 4.9 (0.7) | 3.6 (0.7) | 4.0 (0.9) | 0.7 (0.5) |
| 2 | 9.6 (0.5) | 6.3 (0.5) | 2.8 (0.4) | 2.7 (0.5) | 1.8 (0.5) |
| 3 | 14.1 (0.8) | 4.1 (0.6) | 2.5 (0.6) | 2.4 (0.7) | 0.4 (0.4) |

Adapted from Colleoni et al (2016).
SE: standard error.
[a] Number of events occurring within a time interval divided by the total years of follow-up during the interval accrued by patients at risk during the interval. Patients may have received no adjuvant treatment or have been treated with adjuvant tamoxifen and/or adjuvant chemotherapy.

**Selection of Extended Endocrine Therapy**
Randomized controlled trials have established that 5 years of tamoxifen improves mortality in women with hormone receptor-positive breast cancer. A 2011 individual patient data meta-analysis by the Early Breast Cancer Trialists' Collaborative Group, including 20 trials (total N=21457 patients), found that 5 years of tamoxifen in estrogen receptor-positive disease reduced the relative risk of recurrences by almost 50% over 10 years; breast cancer mortality was decreased by 29% through 15 years.

Early randomized trials of extended tamoxifen treatment: (Tormey et al [1996]; total N=194 patients), the National Surgical Adjuvant Breast and Bowel Project (Fisher et al [2001]; total N=1172 patients), and the Scottish Cancer Trials Breast Group (Stewart et al [2001]; total N=342 patients) had mixed findings. However, more recent available trial evidence suggests that 10 years of tamoxifen in pre- or postmenopausal women can be linked with improved survival (see Table 2).

These randomized controlled trials have shown that extended endocrine therapy decreases the risk of recurrence. The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, which compared 5 and 10 years of tamoxifen, and the subsequent Long-term Effects of Continuing Adjuvant Tamoxifen to 10 Years versus Stopping at 5 Years (aTTom) trial (reported in abstract form) included women who were hormone receptor-positive who had completed 5 years of tamoxifen. Five years of extended tamoxifen was associated with improvements in breast cancer-specific mortality in both ATLAS and aTTom; however, only ATLAS showed improvements in OS (see Table 2).

Several trials have compared survival outcomes in women using extended Aromatase inhibitors versus placebo following several years of tamoxifen, and 2 trials compared the use of extended AIs for different durations (3 years vs. 6 years and 2.5 years versus 5 years) (see Table 2). No differences in OS were detected between the AI groups and the placebo groups. Differences in breast cancer-specific survival were inconsistent. Differences in disease-specific survival and OS were not detected among patients receiving AIs for different lengths of time.

**Adverse Events From Extended Endocrine Therapy**
Adverse events from extended tamoxifen include increased risk of thromboembolic disease (deep vein thrombosis, pulmonary embolism) and endometrial cancer. The ATLAS trial reported relative risks of 1.9 (95% CI, 1.1 to 3.1) for pulmonary embolus and 1.7 (95% CI, 1.3 to 2.3) for endometrial

cancer. Adverse events from extended AIs include musculoskeletal side effects (eg, carpal tunnel syndrome, bone pain, bone fractures). In meta-analyses comparing tamoxifen and AIs, results showed an increased risk in cardiovascular events with AIs relative to tamoxifen. Women treated with AIs have also experienced higher fracture rates compared with women treated with tamoxifen.

**Table 2. Randomized Trials Evaluating Adjuvant Extended Endocrine Therapies for Hormone Receptor-Positive Breast Cancer**

| **Study** | **Population** | **Comparators** | **Breast Cancer-Specific Mortality** | | **Overall Mortality** | |
|---|---|---|---|---|---|---|
| | | | ***Event RR (95% CI)*** | ***p*** | ***Event RR (95% CI)*** | ***p*** |
| **Extended tamoxifen** | | | | | | |
| ATLAS (2013) | 6,846 women with ER-positive, early breast cancer, after 5 y of TAM | Continue TAM to 10 y (n=3428) vs. stop TAM at 5 y (n=3418) | • 0.83 (0.72 to 0.96) (331/3428 vs. 397/3418) | .01 | • 0.87 (0.78 to 0.97)<br>• 722 (639/3428 vs. 722/3418) | .01 |
| aTTom (2013) | 6,953 women with ER-positive or untested breast cancer, after 5 y of TAM | Continue TAM to 10 y (n=3468) vs. stop TAM at 5 y (n=3485) | 10 years<br>• 392/3468 intervention vs. 442/3485 control<br>Years 5-9<br>• 1.03 (0.84 to 1.27) | .05 | 10 years<br>• 849/3468 intervention vs. 910/3485 control<br>Years 5-9<br>• 1.05 (0.90 to 1.22) | .10 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | After year 9<br>• 0.77 (0.64 to 0.92) | | After year 9<br>• 0.86 (0.75 to 0.97) | |
| **Extended aromatase inhibitor** | | | | | | |
| ABCSG (2007) | 856 post-menopausal women with ER- and/or PR-positive breast cancer, after 5 y of TAM | Anastrozole for 3 y (n=386) vs. no further therapy (n=466) | | | 5 years<br>• 10.3% anastrozole vs. 11.7% control<br>Event HR (95% CI)<br>• 0.89 (0.59 to 1.34) | .57 |
| IDEAL (2018) | 1,824 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y endocrine therapy | Letrozole for 2.5 y (n=909) or 5 y (n=915) | Median 6.6 Years<br>• 2.5 and: 82.0%<br>• 5 and: 83.3% | .50 | Median 6.6 Years<br>• 2.5 and: 89.4%<br>• 5 and: 88.6% | NS |
| DATA (2017) | 1,912 post-menopausal women | Anastrozole for 3 y | 5 Years<br>• 3 and: 79.4% | 5 years:.06 | 5 Years<br>• 3 and: 90.4% | 5 years:.60 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | with ER- and/or PR-positive early breast cancer, after 2-3 y TAM | (n=955) or 6 y (n=957) | • 6 and: 83.1%<br>10 Years<br>• 3 and: 66.0%<br>• 6 and: 69.2% | 10 years:.07 | • 6 and: 90.8%<br>10 Years<br>• 3 and: 79.2%<br>• 6 and: 80.9% | 10 years:.53 |
| NSABP (2008) | 1,598 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y of TAM | Planned comparison: 5 y exemestane vs. 5 y placebo. Accrual stopped (N=1598 randomized), and crossover allowed after results of NCIC CTG available: Exemestane: 783 randomized, 560 continued after unblinding Placebo: 779 randomized, | 48 Months<br>• ITT: 91% exemestane vs. 89% placebo | .07 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 334 crossed over to exemestane after unblinding | | | | |
| NCIC CTG MA.17 trial (2003, 2005) | 5,187 post-menopausal women with ER- and/or PR-positive early breast cancer, after 5 y TAM | Continue letrozole to 10 y (n=2593) vs. stop TAM at 5 y (n=2594) | 48 Months<br>• 94.4% letrozole vs. 89.8% placebo<br>Event HR<br>• 0.58 (0.45 to 0.76) | <.001 | 4 8 Months<br>• 95.4% letrozole vs. 95% placebo<br>Event HR<br>• 0.82 (0.57 to 1.19) | .30 |
| SALSA NCT00295620 Gnant et al (2021) | 3,470 post-menopausal women with hormone-receptor-positive early stage breast cancer who had received 5 years of adjuvant endocrine therapy | Aromatase inhibitor for an additional 2 years (total 7 years) vs. an additional 5 years (total 10 years) | Disease recurrence or death<br>10 years: 73.6% vs. 73.9%<br>HR 0.99 (95% CI 0.85 to 1.15) | .90 | 10 years: 87.5% vs. 87.3%<br>HR 1.02 (0.83 to 1.25) | NS |

ABCSG: Austrian Breast and Colorectal Cancer Study Group; CI: confidence interval; DATA: Different Durations of Adjuvant Anastrozole Therapy; ER: estrogen receptor; HR: hazard ratio; IDEAL: Investigation on the Duration of Extended Adjuvant Letrozole; ITT: intention to treat; NCIC CTG: National Cancer Institute Clinical Trials Group; NS: not significant; NSABP: National Surgical Adjuvant Breast and Bowel Project; PR: progesterone receptor; RR: rate ratio; SALSA: Secondary Adjuvant Long-Term Study with Arimidex [anastrozole]; TAM: tamoxifen

**Decision Framework for Evaluating Breast Cancer Biomarkers**

**Simon et al Framework**

Many studies have investigated individual biomarkers or combinations of biomarkers associated with breast cancer outcomes. Determining which studies constitute sufficient evidence that the test or biomarker is likely to be clinically useful depends on attributes of the test such as its performance and the quality of the study generating the results. Simon et al (2009) have described a framework to evaluate prognostic biomarker evidence. Study designs, such as prospective clinical trials or previously conducted clinical trials with archived tumor samples, constitute stronger evidence than studies with less planned and systematic patient recruitment and data collection. Randomized trials allow the determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcomes in the patient group of interest that would result in a change in management (eg, withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show the consistency of results and more than 1 study demonstrating the desired result should be available. Simon et al (2009) have proposed that at least 2 Simon et al (2009) category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker. Simon et al (2009) also proposed that while "further confirmation in a separate trial of the results gained from a category A prospective trial is always welcome, compelling results from such a trial would be considered definitive and no other validating trial would be required."

# FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

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.

**Table 3. Gene Expression Tests Reporting Recurrence Risk for Breast Cancer Considered Herein**

| Test | Manufacturer | Description |
|---|---|---|
| Oncotype DX®‡ | Genomic Health | 21-gene RT-PCR; identifies 3 groups as low, intermediate, and high-risk for distant recurrence |
| EndoPredict®‡ | Sividon Diagnostics (acquired by Myriad in 2016) | 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 |
| Breast Cancer Index SM‡ Prognostic | Biotheranostics | Combines MGI and the HOXB13: IL17BR Index measured using RT-PCR; identifies 2 groups as low or high-risk for distant recurrence |
| MammaPrint®‡ | Agendia | 70-gene DNA microarray; identifies 2 groups as low or high-risk for distant recurrence |
| Prosigna®‡ | NanoString Technologies | 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) |
| Insight TNBCtype™‡ | Insight Genetics | Uses next-generation sequencing of 101 genes to generate 5 molecular subtypes, as well as a complementary immunomodulatory classifier to help predict response to immuno-oncology therapies. This may include directing selection and combination of chemotherapies, as well as to support development of novel TNBC targeted therapeutics and diagnostics |

| | | |
|---|---|---|
| DCISionRT | PreludeDx | Combines 7 monoclonal protein markers (COX-2, FOXA1, HER2, Ki-67, p16/INK4A, PR, and SIAH2) assessed in tumor tissue with 4 clinicopathologic factors (age at diagnosis, tumor size, palpability, and surgical margin status) to produce a score that stratifies individuals with DCIS into 3 risk groups: low risk, elevated risk with good response, and elevated risk with poor response. The purpose of the test is to predict radiation benefit in individuals with DCIS following breast conserving surgery. |

DCIS: ductal carcinoma in situ; 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.

# Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

**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 (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.

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

**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 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.

***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.

# Supplemental Information

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

**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 4.

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 4. 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 | High | Strong |

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| | for adjuvant endocrine and chemotherapy | | |
| | 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 |

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| | 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 | Insufficient | Moderate |

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| | nodes, the clinician should not use EndoPredict®‡ test to guide decisions for adjuvant endocrine and chemotherapy | | |
| | 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 | Insufficient | Strong |

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|---|---|---|---|
| | decisions for adjuvant endocrine and chemotherapy is insufficient to recommend its use | | |
| ***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 | Intermediate | Strong |

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|---|---|---|---|
| | endocrine therapy with either tamoxifen, an AI or a sequence of tamoxifen followed by AI | | |
| 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)

**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. 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.
- Importantly, neither ASCO nor NCCN guidelines currently imply the superiority of any one genomic test over another.
- 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 4.2023. 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 September 25, 2023, are listed in Table 5.

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 5. National Comprehensive Cancer Network Recommendations on the Use of Biomarker Assays to Guide Adjuvant Systemic Therapy[a], 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 |
| 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 Comprehnsive 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.

**Ongoing and Unpublished Clinical Trials**
Current ongoing and unpublished trials that might influence this review are listed in Table 6.

**Table 6. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| *Ongoing* | | | |
| NCT02889874 | A Randomised Phase III Trial of Adjuvant Radiation Therapy Versus Observation Following Breast Conserving Surgery and Endocrine Therapy in Patients With Molecularly Characterised Luminal A Early Breast Cancer | 1167 | Dec 2023 |
| NCT01272037 | A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients With 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer With Recurrence Score (RS) of 25 or Less. RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer | 5083 | Mar 2024 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| NCT02400190 | The IDEA Study (Individualized Decisions for Endocrine Therapy Alone) | 202 | Mar 2026 |
| NCT02653755[a] | The PRECISION Trial (Profiling Early Breast Cancer for Radiotherapy Omission): a Phase II Study of Breast-Conserving Surgery Without Adjuvant Radiotherapy for Favorable Risk Breast Cancer | 672 | Jun 2026 |
| NCT03917082 | Single arm phase II study exploring reducing the duration of endocrine therapy from five to two years in low risk population with early breast cancer | 290 | May 2029 |
| NCT02476786 | Endocrine Treatment Alone as Primary Treatment for Elderly Patients With Estrogen Receptor Positive Operable Breast Cancer and Low Recurrence Score | 50 | Jan 2030 |
| NCT01805271 | Randomized, Double-Blind, Multicentric Phase III Trial Evaluating the Safety and Benefit of Adding Everolimus to Adjuvant Hormone Therapy in Women With High Risk of Relapse, ER+ and HER2- Primary Breast Cancer Who Remain Free of Disease After Receiving at Least 1 Year of Adjuvant Hormone Therapy | 1278 | Jun 2030 |
| NCT00310180 | Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning Individualized Options for Treatment: The TAILORx Trial | 10,273 | Sep 2030 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| ISRCTN42400492 | Optimal personalised treatment of early breast cancer using multiparameter analysis (OPTIMA) | 4500 | Dec 2031 |
| NCT03503799 | Prospective Assessment of Disease Progression in Primary Breast Cancer Patients Undergoing EndoPredict Gene Expression Testing - a Care Research Study | 1191 | Oct 2032 |
| NCT05634889 | The T-REX-Trial: Tailored Regional External Beam Radiotherapy in Clinically Node-negative Breast Cancer Patients With 1-2 Sentinel Node Macrometastases; an Open, Multicenter, Randomized Non-inferiority Phase 3-tria | 1350 | Dec 2033 |
| NCT04852887 | A Phase III Clinical Trial Evaluating De-Escalation of Breast Radiation for Conservative Treatment of Stage I, Hormone Sensitive, HER-2 Negative, Oncotype Recurrence Score Less Than or Equal to 18 Breast Cancer | 1670 | Jul 2041 |
| NCT03904173 | Establishment of Molecular Profiling for Individual Clinical Routine Treatment Decision in Early Breast Cancer | 2298 | Dec 2043 |

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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## Policy History

Original Effective Date: 03/01/2007
Current Effective Date: 01/08/2024

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|---|---|
| 09/06/2006 | Medical Director review |
| 09/20/2006 | Medical Policy Committee approval |
| 10/03/2007 | Medical Director review |
| 10/17/2007 | Medical Policy Committee approval. Policy Statements Changed. Oncotype DX eligible for coverage. Not medically necessary statement added. |
| 02/13/2008 | Medical Director review |
| 02/20/2008 | Medical Policy Committee approval. Policy statement changed to include patient selection criteria. Added 21-gene RT-pcr assay Oncotype DX . |
| 02/04/2009 | Medical Director review |
| 02/19/2009 | Medical Policy Committee approval. Clarified 6th and 7th criteria bullets. No change to coverage eligibility. |
| 02/04/2010 | Medical Policy Committee review |
| 02/17/2010 | Medical Policy Implementation Committee approval. No change to coverage. |

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| 02/03/2011 | Medical Policy Committee review |
| 02/16/2011 | Medical Policy Implementation Committee approval. New criteria added. |
| 02/02/2012 | Medical Policy Committee review |
| 02/15/2012 | Medical Policy Implementation Committee approval. Rationale extensively revised. Coverage eligibility unchanged. |
| 02/07/2013 | Medical Policy Committee review |
| 02/20/2013 | Medical Policy Implementation Committee approval. Added the BreastOncPx and the PAM50 Breast Cancer Intrinsic Classifier as examples of investigational gene expression assays. |
| 04/02/2015 | Medical Policy Committee review |
| 04/20/2015 | Medical Policy Implementation Committee approval. Added investigational statements to include newer assays (prosignia, BluePrint, TargetPrint, EndoPredict, MammaPrint, Mammostrat, NexCourse, Oncotype DCIS) and use of gene assays in men. Updated FDA, rationale and references. |
| 10/08/2015 | Medical Policy Committee review |
| 10/21/2015 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/01/2016 | Coding update |
| 10/06/2016 | Medical Policy Committee review |
| 10/19/2016 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 01/05/2017 | Medical Policy Committee review |
| 01/18/2017 | Medical Policy Implementation Committee approval. EndoPredict, Breast Cancer Index and Prosigna removed from investigational statement. Coverage statement added that these tests are medically necessary for same indication as Oncotype. Coverage statement clarified with "primary, invasive" and investigational statement clarified with "length of treatment with tamoxifen." |
| 01/04/2018 | Medical Policy Committee review |
| 01/17/2018 | Medical Policy Implementation Committee approval. Added a "*Note"* after the eligible for coverage section that only one assay of genetic expression per tumor tissue specimen will be eligible for coverage. Coverage eligibility unchanged. |
| 07/01/2018 | Coding update |
| 01/10/2019 | Medical Policy Committee review |

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| 01/23/2019 | Medical Policy Implementation Committee approval. Policy statement was changed for indications pertaining to adjuvant chemotherapy by adding MammaPrint to the list of tests which are considered "medically necessary". Change the example in the investigational statement regarding predicting recurrence from "Oncotype DX DCIS" to "Oncotype DX Breast DCIS Score". Removed the investigational statement for 70-gene signature (MammaPrint).Added a Policy Guidelines section and a reference to the Policy Guidelines in the Patient Selection Criteria. |
| 01/03/2020 | Medical Policy Committee review |
| 01/08/2020 | Medical Policy Implementation Committee approval. Eligible for coverage statement with criteria added for MammaPrint assay to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer. Additional criteria for MammaPrint added for stage T1 or T2 or operable T3, and for node-negative lymph nodes. |
| 01/07/2021 | Medical Policy Committee review |
| 01/13/2021 | Medical Policy Implementation Committee approval. Combined MammaPrint with the other 4 assays as eligible for coverage with criteria. Deleted the separate eligible for coverage with criteria section for MammaPrint. Changed the tumor size to > 0.5 cm (stage T1b- T3) in the 4th criteria bullet. Changed the 5th criteria bullet to read: "Node negative (lymph nodes with micrometastases [ 2 mm in size] are considered node negative for this policy statement) OR one to three positive lymph nodes". Removed, "(except as allowed for MammaPrint)" from the 1st investigational statement. Added "more than three" to indicate the number of positive lymph nodes to the 1st investigational statement. Investigational statement added for the use of Insight TNBCtype to aid in making decisions regarding chemotherapy in women with triple-negative breast cancer. Removed the Policy Guidelines section. |
| 12/20/2021 | Coding Update |
| 01/06/2022 | Medical Policy Committee review |
| 01/12/2022 | Medical Policy Implementation Committee approval. Added "Eligible for coverage" to describe assays in the "When Services May Be Eligible for Coverage" section Tamoxifen changed to endocrine therapy (tamoxifen or aromatase inhibitors) in the first investigational statement. |
| 03/25/2022 | Coding update |

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

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/08/2024

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| 10/06/2022 | Medical Policy Committee review |
| 10/11/2022 | Medical Policy Implementation Committee approval. Extensive revisions made to the coverage section. |
| 12/01/2022 | Medical Policy Committee review |
| 12/14/2022 | Medical Policy Implementation Committee approval. Revised the first set of Patient Selection Criteria and the first investigational statement. Added a Policy Guidelines section. |
| 12/07/2023 | Medical Policy Committee review |
| 12/13/2023 | Medical Policy Implementation Committee approval. Revised the first set of Patient Selection Criteria. Coverage eligibility for only one assay of genetic expression per tumor tissue specimen is specified per indication. Removed "postmenopausal" requirement from the eligible for coverage statement for the use of the Breast Cancer Index (BCI)SM‡ assay predict risk of late distant recurrence (years 5-10) and benefit of extended adjuvant endocrine therapy in women with primary, invasive breast cancer. Revised the investigational statement for all other indications for the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay by adding "when BCI was not used before" regarding testing for breast cancer patients. Updated NCCN information from Version 4.2023 in the Supplemental Information section. References updated for CMS, CDC, and NCCN. |

Next Scheduled Review Date: 12/2024

# Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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

Policy # 00211
Original Effective Date: 03/01/2007
Current Effective Date: 01/08/2024

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|---|---|
| CPT | 0045U, 0153U, 81479, 81518, 81519, 81520, 81521, 81522, 81523<br>81599, 88399, 84999 |
| HCPCS | S3854 |
| ICD-10 Diagnosis | All related Diagnoses |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.