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

Policy # 00211
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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‡, and Prosigna®‡ to determine recurrence risk for deciding whether 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 RT-PCR assay (i.e., Oncotype DX), EndoPredict®‡, the Breast Cancer Index (BCI)SM‡, and Prosigna®‡ to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy in women with breast cancer will be considered when ALL of the following criteria are met:

- Unilateral tumor, AND
- Hormone receptor positive (i.e., estrogen receptor-positive [ER+] or progesterone receptor-positive [PR+]); AND
- Human epidermal growth factor receptor 2 (HER2)-negative; AND
- Tumor size 0.6–1 cm with moderate/poor differentiation or unfavorable features (see Policy Guidelines) OR tumor size greater than 1 cm; AND
- Node negative (lymph nodes with micrometastases (less than 2 mm in size) are considered node negative for this policy statement); AND

- Who will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors 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.

Based on review of available data, the Company may consider the use of MammaPrint®‡ assay to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer may be to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of MammaPrint assay to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer will be considered when ALL of the following criteria are met:

- Unilateral tumor; AND
- Hormone receptor-positive (ie, estrogen receptor-positive or progesterone receptor-positive); AND
- Human epidermal growth factor receptor 2-negative; AND
- Stage T1 or T2 (tumor size is not more than 5 cm across) OR operable T3 (tumor is more than 5 cm across, however not growing into the chest wall or skin, and not an inflammatory breast cancer) at high clinical risk (see Policy Guidelines for high clinical risk); AND
- 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; AND
- Who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors); AND
- 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.

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 will be eligible for coverage.

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 RT-PCR assay (i.e., Oncotype DX), EndoPredict, the Breast Cancer Index (BCI), MammaPrint, and Prosigna, including determination of recurrence risk in invasive breast cancer patients with positive lymph nodes (except as allowed for MammaPrint), patients with bilateral disease or to consider length of treatment with tamoxifen to be **investigational.***

Based on review of available data, the Company considers 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 ([DCIS]; ie, Oncotype DX Breast DCIS Score) to inform treatment planning after excisional surgery 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.***

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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 gene expression assays in men with breast cancer to be **investigational.***

Policy Guidelines

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

- Grade: well differentiated; tumor size, <= 2 cm or 2.1 to 5 cm
- Grade: moderately differentiated; tumor size, any size
- Grade: poorly differentiated or undifferentiated; tumor size, any size

Background/Overview

Newly Diagnosed Breast Cancer

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 three 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 the 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 five to ten years for women who are hormone receptor-positive but HER2-negative and who have survived without a recurrence for five 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 five to ten years after an initial diagnosis has support in clinical practice. The guidelines from the National Comprehensive Cancer Network (v.1.2019) do not recommend extended endocrine therapy, but state that AIs or tamoxifen *may be considered* following 5 years of endocrine therapy for certain women, depending on menopausal status and prior treatment history The guidelines also note that the optimal duration of AIs is uncertain. The American Society for Clinical Oncology (2018) updated its guidelines from 2014 on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. The update included a qualifying statement that none of the studies used to develop the recommendations showed improvements in overall survival (OS) with extended therapy, and that the recommendations are based on benefits that include prevention of distant recurrence and prevention of second breast cancers. Therefore, the decision to receive extended therapy should involve the weighing of recurrence risk against potential therapy risks and side effects. Recommendations based on nodal status are as follows:
    - "Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine therapy based on considerations of recurrence risk using established prognostic factors. However, as recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.

- Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine therapy."

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.

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 five 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 ten 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 five and ten 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 five 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 AIs aromatase inhibitors vs placebo following several years of tamoxifen, and two trials compared the use of extended AIs for different durations (3 years vs 6 years and 2.5 years vs 5 years) (see Table 2). No differences in OS were detected between the AI groups and with 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.

Guidelines for Extended Endocrine Therapy
For patients with early-stage, invasive breast cancer that is hormone receptor-positive, the use of endocrine therapy (tamoxifen and/or an AI, with or without ovarian suppression) for the initial five years following initial diagnosis has support in national guidelines. Support for extended endocrine therapy beyond the initial five years is inconsistent across various guidelines.

The latest guidelines from the American Society for Clinical Oncology (2014) discuss extended endocrine therapy for breast cancer have recommended an additional 5 years of tamoxifen for premenopausal women and 5 years of AIs for postmenopausal women. National Comprehensive Cancer Network guidelines (v.3.2019) do not recommend extended endocrine therapy, but state that AIs or tamoxifen may be considered following 5 years of endocrine therapy. The guidelines also note that the optimal duration of aromatase inhibitors is uncertain.

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)	6846 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)	0.01	• 0.87 (0.78 to 0.97) • 722 (639/3428 vs 722/3418)	0.01
aTTom (2013)	6953 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 • 392/3468 intervention vs 442/3485 control Years 5-9 • 1.03 (0.84 to 1.27) After year 9 • 0.77 (0.64 to 0.92)	0.05	10 years • 849/3468 intervention vs 910/3485 control Years 5-9 • 1.05 (0.90 to 1.22) After year 9 • 0.86 (0.75 to 0.97)	0.1
Extended aromatase inhibitor						
ABCSG (2007)	856 post-menopausal women	Anastrozole for 3 y (n=386) vs no			5 years	0.57

Study	Population	Comparators	Breast Cancer-Specific Mortality		Overall Mortality	
	with ER- and/or PR-positive breast cancer, after 5 y of TAM	further therapy (n=466)			• 10.3% anastrozole vs 11.7% control Event HR (95% CI) • 0.89 (0.59 to 1.34)	
			Breast Cancer-Specific Survival		*Overall Survival*	
IDEAL (2018)	1824 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 • 2.5 y: 82.0% • 5 y: 83.3%	0.5	Median 6.6 Years • 2.5 y: 89.4% • 5 y: 88.6%	*NS*
DATA (2017)	1912 post-menopausal women with ER- and/or PR-positive early breast cancer, after 2-3 y TAM	Anastrozole for 3 y (n=955) or 6 y (n=957)	5 Years • 3 y: 79.4% • 6 y: 83.1%	0.06	5 Years • 3 y: 90.4% • 6 y: 90.8%	0.6

Study	Population	Comparators	Breast Cancer-Specific Mortality		Overall Mortality	
NSABP (2008)	1598 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, 334 crossed over to exemestane after unblinding	48 Months • ITT: 91% exemestane vs 89% placebo	0.07		
NCIC CTG MA.17 trial (2003, 2005)	5187 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 • 94.4% letrozole vs 89.8% placebo Event HR • 0.58 (0.45 to 0.76)	<0.001	48 Months • 96% letrozole vs 94% placebo Event HR • 0.76 (0.48 to 0.21) 40 Months • 95.4% letrozole vs 95% placebo Event HR • 0.82 (0.57 to 1.19)	0.25 0.3

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; TAM: tamoxifen.

In addition to the trials published in full-length form, 2 trials were presented in early 2017 evaluating extended endocrine therapy in postmenopausal women (NSABP-42 [NCT00382070]: 10 years vs 5 years of letrozole; and IDEAL [NTR3077] 10 years vs 7.5 years of letrozole) did not meet their primary endpoints.

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 one 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."

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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) and EndoPredict (distributed by Myriad) are not FDA-approved.

Rationale/Source

Laboratory tests have been developed to detect the expression, via messenger RNA, of different genes in breast tumor tissue and combine the results into a prediction of distant recurrence risk for women with early-stage breast cancer. Test results may help providers and patients decide whether to include adjuvant chemotherapy in the postsurgical management of breast cancer, to alter treatment in patients with ductal carcinoma in situ (DCIS), or to recommend extended endocrine therapy in patients who are recurrence-free at five years. This report summarizes the evidence for five tests, which are organized by indication: Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna.

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

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

Oncotype DX (21-Gene Assay)
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes multiple prospective clinical trials and prospective-retrospective studies. Patients classified as low-risk with Oncotype DX have a low risk of recurrence in which avoidance of adjuvant chemotherapy is reasonable (average risk at 10 years, 3%-7%; upper bound of the 95% confidence interval [CI], 6% to 10%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

EndoPredict
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes three prospective-retrospective studies and observational studies. The studies revealed that a low score was associated with a low absolute risk of 10-year distant recurrence (average risk at 10 years for the 2 larger studies, 3%-6%; upper bound of the 95% CI, 6% to 9%). Over half of the patients in these studies were classified as low-risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Cancer Index
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the Breast Cancer Index, the evidence

includes findings from two prospective-retrospective studies and a registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk Breast Cancer Index score is associated with low 10-year distant recurrence rates (average risk at 10 years, 5%-7%; upper bound of the 95% CI, 8% to 10%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

MammaPrint (70-Gene Signature)
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a prospective-retrospective study and a randomized controlled trial providing evidence for clinical utility. The prospective-retrospective study reported high 10-year distant metastases-free survival for the low-risk group treated with tamoxifen (93%; 95% CI, 88% to 96%), but not as high survival for the low-risk group not treated with tamoxifen (83%, 95% CI, 76% to 88%). The randomized controlled trial Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy showed five-year distance recurrence rates below the 10% threshold among patients identified as low-risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Prosigna
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Prosigna, the evidence includes two prospective-retrospective studies evaluating the prognostic ability of Prosigna. Both studies showed a low absolute risk of distant recurrence in patients with low-risk scores (average risk at 10 years, 3%-5%; upper bound 95% CI, 6%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Early-Stage Node-Positive (1 to 3 Nodes) Invasive Breast Cancer
For decisions on the management of early-stage node-positive disease, Oncotype DX, EndoPredict, MammaPrint, and Prosigna were evaluated. Only studies presenting a minimum of five-year distant recurrence rates or five-year survival rates were included in this part of the evidence review.

Oncotype DX (21-Gene Assay)
For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes 3 prospective-retrospective studies. The prospective-retrospective studies showed that Oncotype DX stratifies node-positive patients into high- and low-risk for distant recurrence-free survival. The studies have proposed different cutoffs for low-risk. One of the studies with a recurrence score cutoff for low-risk of 18 reported CIs for estimates and those are very wide. The analysis from the Plan B study included patients with node-negative and node-positive breast cancer. The authors reported that subgroup analyses of patients with node-positive breast cancer who were classified as low-risk (recurrence score <=11) experienced higher rates of survival than patients classified as high-risk, though no rates were provided. Five-year DFS in patients with one positive node and recurrence score <=11 treated with endocrine therapy alone (n=110) was 94.4% (95% CI, 89.5 to 99.3%). There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy but consensus on cutoffs and accurate risk estimates are needed to inform patient decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

MammaPrint (70-Gene Signature)
For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a clinical utility study. The randomized controlled trial Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy showed 5-

year distance recurrence rates below the 10% threshold among node-positive (one to three nodes) patients identified as low-risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Ductal Carcinoma In Situ
The Oncotype DX Breast DCIS Score is the only assay investigated for patients with DCIS.

Oncotype DX Breast DCIS Score
For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS Score, the evidence includes a prospective-retrospective study and a retrospective cohort study. Although the studies have shown that the test stratifies patients into high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in patients identified with a Breast DCIS Score is low enough to consider changing the management of DCIS. The evidence is insufficient to determine the effects of the technology on health outcomes.

Extended Endocrine Therapy
For this indication, Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna were evaluated. Studies retrospectively collecting tumor samples from prospective trials that

provided ten-year distant recurrence rates or ten-year survival rates were included in this part of the evidence review. Studies comparing genetic assays with clinical risk prediction tools were also included.

Oncotype DX (21-Gene Assay)
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes 2 studies using data from the same previously conducted clinical trial. One analysis did not provide CIs and the other study reported a distant recurrence rate of 4.8% (95% CI, 2.9% to 7.9%) for the low-risk group. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

EndoPredict
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at five years who are considering extending endocrine treatment who receive gene expression profiling with EndoPredict, the evidence includes two analyses of archived tissue samples from two previously conducted clinical trials. The studies showed low distant recurrence rates in patients classified as low-risk with EndoPredict. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported 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 reporting on the association between risk score and survival are needed to confirm results from the single study. More importantly, clarity is needed about how the test would inform clinical practice. The evidence is insufficient to determine the effects of the technology on health outcomes.

Breast Cancer Index
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at five years who are considering extending tamoxifen treatment who receive gene expression profiling with the Breast Cancer Index, the evidence includes three analyses of archived tissue samples from two previously conducted clinical trials and a retrospective cohort study. The analyses showed low distant recurrence rates and high distant recurrence-free survival rates in patients classified as low-risk with the test. Two studies suggested that, in addition to having a more

favorable prognosis, low-risk patients may receive less benefit from extended endocrine therapy. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

MammaPrint (70-Gene Signature)
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a retrospective-prospective study. Analyses on patients classified as ultralow-risk (a subgroup of the low-risk group) showed that this ultralow-risk group experienced high 10- and 20-year breast cancer-specific survival rates. Additional studies are needed to confirm the results of this single study. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at five 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 three publications. The studies showed low distant recurrence rates in patients classified as low-risk with the test. A reclassification result suggested that the test may offer little improvement over clinical predictors alone. Clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

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.

In response to requests, input was received from 1 physician specialty society and 4 academic medical centers while this policy was under review in 2008. A clear majority of reviewers agreed with the policy conclusions.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Adjuvant Chemotherapy for Node-Negative Breast Cancer
Current guidelines from the NCCN for breast cancer (v.3.2019) provide a summary table assessing multigene assays to inform the addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy (page BINV-N). The table shows that several genetic assays can be used to identify patients with node-negative breast cancer and low recurrence risk scores who may derive little benefit from chemotherapy. The NCCN category of evidence and consensus for the following assays is level 1 for Oncotype DX and MammaPrint, and level 2A for Prosigna, EndoPredict, and the Breast Cancer Index. In the table, NCCN states that all the tests are prognostic, but only the Oncotype DX is predictive of response to chemotherapy in patients with node-negative breast cancer and is the preferred testing of the Network panel. In addition to the summary table, the following recommendation appears in an algorithm:

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

Adjuvant Chemotherapy for Node-Positive Breast Cancer
The table discussed above in the NCCN guidelines for breast cancer (v.3.2019) also provides information on the use of genetic assays to inform recurrence risk for patients with node-positive (1 to 3 nodes) breast cancer. The level of evidence and consensus for MammaPrint for this population is 1 and the level of evidence and consensus for Oncotype DX and EndoPredict for this population is 2A. In addition to the summary table, the following recommendation appears in an updated algorithm:

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

Extended Endocrine Therapy

The latest NCCN guideline (v.3.2019) provides a flow chart on adjuvant endocrine therapy (aromatase inhibitors [AI] or tamoxifen) recommendations and considerations, based on menopausal status at diagnosis and after 5 years of therapy, and on prior therapy history (page BINV-K). The following Table 3 summarizes the contents of the flow chart:

Table 3. NCCN Recommendations and Considerations for Extended Endocrine Therapy

Menopausal Status at Diagnosis	Therapy History	Current Menopausal Status	Recommendations or Considerations
Premenopausal	• Tamoxifen 5 years (category 1) • AI 5 years (category 1)	Postmenopausal	• Recommend AI 5 more years (category 1) • Consider tamoxifen 5 more years
Premenopausal	• Tamoxifen 5 years (category 1) • AI 5 years (category 1)	Premenopausal	• Consider tamoxifen 5 years • No further endocrine therapy

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

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

American Society of Clinical Oncology

The American Society of Clinical Oncology (2017) updated its evidence-based guidelines on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer and published a focused update of those guidelines in 2019. The ASCO also updated endorsement of the Cancer Care Ontario recommendations on the Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer in 2019. The recommendations are consistent with the table below. Table 4 shows the gene expression profiling biomarkers found to have demonstrated clinical utility to guide decisions on the need for

adjuvant systemic therapy in women with early-stage invasive breast cancer and known estrogen and progesterone and *HER2* status. The guidelines did not endorse any test for decision-making to determine the length of tamoxifen treatment.

Table 4. Guidelines for Estrogen and Progesterone Receptor-Positive and *HER2*-Negative Breast Cancer

Test	Recommendation	QOE	SOR
Node-negative			
Oncotype DX	"For patients older than 50 years and whose tumors have Oncotype DX recurrence scores of less than 26, and for patients age 50 years or younger whose tumors have Oncotype DX recurrence scores of less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone."	High	Strong
	"For patients age 50 years or younger with Oncotype DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy"	Intermediate	Moderate
	"Patients with Oncotype DX recurrence scores of greater than 30	High	Strong

Test	Recommendation	QOE	SOR
	should be considered candidates for chemoendocrine therapy"		
	"..oncologists may offer chemoendocrine therapy to patients with Oncotype DX scores of 26 to 30"	Insufficient	Moderate
EndoPredict	Clinician may use the 12-gene risk score to guide decisions on adjuvant systemic chemotherapy	Intermediate	Moderate
Breast Cancer Index	Clinician may use the Breast Cancer Index to guide decisions on adjuvant systemic therapy	Intermediate	Moderate
MammaPrint	• Clinician may use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization • Clinician should **not** use the 70-gene assay to guide decisions on adjuvant systemic therapy in women with low clinical risk per MINDACT categorization	High	Strong

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

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

St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer
In 2017, an international expert Panel, including members from the U.S., convened for the 15th St. Gallen International Breast Cancer Conference. The Panel reviewed current evidence on locoregional and systemic therapies for early breast cancer. Table 5 summarizes relevant recommendations.

Table 5. Therapies by Breast Cancer Diagnosis

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

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.

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: 01/08/2020

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			
NCT00310180	Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning Individualized Options for Treatment: The TAILORx Trial	10,273	Sep 2030
NCT00433589[a]	MINDACT (Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy): A Prospective, Randomized Study Comparing the 70-Gene Signature With the Common Clinical-Pathological Criteria in Selecting Patients for Adjuvant Chemotherapy in Breast Cancer With 0 to 3 Positive Nodes	6600	Mar 2020

NCT No.	Trial Name	Planned Enrollment	Completion Date
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	10,000	Feb 2022
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	690	Jun 2023
NCT02889874	A Randomised Phase III Trial of Adjuvant Radiation Therapy Versus Observation Following Breast Conserving	1167	Dec 2023

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Surgery and Endocrine Therapy in Patients With Molecularly Characterised Luminal A Early Breast Cancer		
NCT02400190	The IDEA Study (Individualized Decisions for Endocrine Therapy Alone)	202	Mar 2026
NCT03503799	Prospective Assessment of Disease Progression in Primary Breast Cancer Patients Undergoing EndoPredict Gene Expression Testing - a Care Research Study	1200	May 2031
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-	1984	Jun 2031

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Primary Breast Cancer Who Remain Free of Disease After Receiving at Least 1 Year of Adjuvant Hormone Therapy		
ISRCTN42400492	Optimal personalized treatment of early breast cancer using multiparameter analysis (OPTIMA)	4500	Sep 2023
NCT03904173	Establishment of Molecular Profiling for Individual Clinical Routine Treatment Decision in Early Breast Cancer	2150	Dec 2043

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

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Policy History

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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.

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

Policy # 00211
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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 to track BCBSA 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.

Next Scheduled Review Date: 01/2021

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 2019 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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Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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

Code Type	Code
CPT	0045U, 81518, 81519, 81520, 81521 Code added eff 1/1/2020: 0153U, 81522
HCPCS	S3854
ICD-10 Diagnosis	C50.011-C50.019, C50.111-C50.119, C50.211-C50.219, C50.311-C50.319, C50.411-C50.419, C50.511-C50.519, C50.611-C50.619, C50.811-C50.819, C50.911-C50.919, C50.021-C50.029, C50.121-C50.129, C50.221-C50.229, C50.321-C50.329, C50.421-C50.429, C50.521-C50.529, C50.621-C50.629, C50.821-C50.829, C50.921-C50.929, D05.00-D05.02, D05.10-D05.12, D05.80-D05.82, D05.90-D05.92

*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:

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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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