Assays of Genetic Expression to Determine Prognosis of Breast Cancer

Newly Diagnosed Breast Cancer
Most women with newly diagnosed breast cancer in the United States present with early-stage or locally advanced (i.e., 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 level 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 3 decision points:

1. **The decision to pursue adjuvant chemotherapy following locoregional therapy, with or without neoadjuvant chemotherapy, based on 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 balanced 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, we focus specifically on patients without HER2 expression.

2. **The decision to pursue adjuvant endocrine therapy from 5 to 10 years for women who are hormone receptor-positive but HER2-negative and who have survived without recurrence to 5 years.** For patients with hormone receptor-positive tumors, the use of adjuvant endocrine therapy (tamoxifen and/or an aromatase inhibitor, with or without ovarian suppression) for 5 to 10 years after an initial diagnosis has support in clinical practice. The 2017 guidelines from the National Comprehensive Cancer Network (NCCN) recommend extended endocrine therapy. The American Society for Clinical Oncology’s (ASCO) 2014 focused update to its guidelines on adjuvant endocrine therapy for women with hormone receptor–positive breast cancer have recommended 10 years of tamoxifen for pre- or perimenopausal women, and a total of 7-8 to 10 years of endocrine therapy, following 1 of 4 regimens that include tamoxifen with or without an aromatase inhibitor for postmenopausal women.

3. **The decision to pursue adjuvant radiotherapy in women with ductal carcinoma in situ**
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(DCIS). 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. Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy. These women have an approximately 15% ten-year risk of recurrence with tamoxifen alone; 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 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.

Selection of Extended Endocrine Therapy
Randomized controlled trials have established that 5 years of tamoxifen improves mortality in women with hormone receptor-hormone receptor breast cancer. A 2011 individual patient data meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group, including 20 trials (total N=21,457 patients) found that 5 years of tamoxifen in estrogen receptor-positive disease reduced the risk of recurrences by almost 50% over 10 years on the relative scale; breast cancer mortality was decreased by 29% through 15 years.

For patients with early-stage, invasive breast cancer that is hormone receptor-positive, the use of endocrine therapy (tamoxifen and/or aromatase inhibitor, with or without ovarian suppression) for 5 to 10 years following initial diagnosis has support in national guidelines. However, the regimens available and the evidence to support them vary.

Randomized controlled trials published recently have shown that extended endocrine therapy decreases the risk of recurrence. The ASCO and NCCN guidelines were informed primarily by results of the ATLAS trial, which compared 5 and 10 years of tamoxifen and the subsequent aTTom trial (reported in abstract form). In both trials, in women who were hormone receptor-positive and had completed 5 years of tamoxifen, 5 years of extended tamoxifen was associated with improvements in breast cancer-specific mortality; ATLAS showed improvements in overall survival.

Three previously reported randomized trials of extended tamoxifen treatment had mixed findings: Tormey et al (1996; total N=194 patients),10 the National Surgical Adjuvant Breast and Bowel Project (Fisher et al, 2001; total N=1172 patients),11 and the Scottish Cancer Trials Breast Group (Stewart et al, 2001; total N=342 patients).

Overall, the available trial evidence would suggest that 10 years of tamoxifen in pre-or postmenopausal women can be linked with improved survival while trials of extended aromatase inhibitors in different populations of hormone receptor-positive patients have had more mixed results.
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In addition to the trials published in full-length form, 3 trials presented in early 2017 evaluating extended endocrine therapy in postmenopausal women (NSABP-42 [NCT00382070]: 10 years vs 5 years of letrozole; DATA [NCT00301457]: 6 years vs 3 years of anastrozole; and IDEAL [NTR3077] 10 years vs 7.5 years of letrozole) did not meet their primary end points.

Clinical Uses Of Gene Expression Signatures For Breast Cancer

In other clinical scenarios involving breast cancer, accurate assessment of prognosis may affect the decision to offer certain treatments. Recently, several groups have identified panels of gene expression markers (“signatures”) that appear to predict the baseline risk of invasive breast cancer recurrence after surgery, radiotherapy, and endocrine therapy (for hormone receptor to positive tumors).

Several gene expression tests commercially available in the United States include Oncotype DX® (21 Gene RT-PCR) by Genomic Health; EndoPredict® (12 gene real-time RT-PCR by Sividon Diagnostics/Myriad); Breast Cancer Index Prognosticsm (combines JGI and the HOXB13:IL17BR Index measured using RT-PCR) by bioTheranostics; MammaPrint® (70 gene DNA microarray) by Agendia; and Prosigna® (gene expression signature Predictive signature based on nCounter® digital analysis system based on PAM50 breast cancer Intrinsic subtype classifier) by NanoString Technologies. If these panels are more accurate risk predictors than current conventional classifiers, they could be used to aid decision making on adjuvant treatments without greatly affecting disease-free survival and overall survival (OS).

This review focuses on gene expression profiling panels that have prognostic or predictive ability in individuals with early-stage, invasive breast cancer with known estrogen receptor and progesterone receptor and human epidermal growth factor receptor (HER2) status. The proposed clinical utility of these tests varies by the clinical context; these specific indications are discussed in this review:

1. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, hormone receptor-positive, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.
2. Prognosis and/or prediction of treatment response in patients with node-positive (1-3 nodes), hormone receptor-positive, early-stage, HER2-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.
3. Prognosis and/or prediction of treatment response in patients with DCIS for the purpose of determining whether patients can avoid radiotherapy.
4. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, hormone receptor-positive, HER2-negative invasive breast cancer, receiving adjuvant hormonal therapy, who have survived without progression to 5 years postdiagnosis, for the purpose of determining whether patients will continue adjuvant hormonal therapy.

For each of these indications, clinical trials have shown that there is some clinical benefit to receiving the additional therapy under consideration. However, each additional treatment has potential adverse effects. If a patient subgroup can be defined that has an extremely low risk of distant recurrence, or a subgroup can be defined that does not respond to the treatment, then the additional treatment can be forgone with little effect on cancer outcome due to the low risk of poor outcome or lack of response to treatment.

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
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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 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 has proposed that at least 2 Simon category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker.

Breast Cancer-Specific Outcomes

The main outcome of interest for this review is 10-year distant recurrence-free survival. Distant recurrence is a hallmark of advanced breast cancer and thus more informative of OS than disease-free survival. Disease-free survival also includes local recurrence, which has a much better treatment prognosis than distant disease. For the extended endocrine indications in this review, the main outcome of interest is 10-year distant recurrence-free survival conditional on recurrence-free survival for 5 years.

Decisions to undergo or forgo adjuvant therapy (chemotherapy or endocrine) depend on how a woman values the potential benefit of lower recurrence risk relative to the harms of treatment. The balance of benefits and harms determines the thresholds that inform decisions. Most women will accept substantial adverse events for even modest benefit. For example, Simes et al (2001) interviewed 104 Australian women with breast cancer treated with cytotoxic chemotherapy and elicited preferences to undergo chemotherapy according to probable gain in survival.20 With an expected survival of 5 years without chemotherapy, 73% said they would accept chemotherapy for an increased survival of 6 months or less; with an expected survival of 15 years, 39% would accept treatment for a gain of 6 months. Duric et al (2005) found 64% to 84% of 97 women expressing a willingness to undergo chemotherapy for a 1- year improvement in life expectancy or 3% increase in survival rates. About half felt a single day would justify adjuvant chemotherapy. A major difference between the 2 studies was that the chemotherapy regimen in Duric et al was less toxic. Thewes et al (2005) adopted the same approach for adjuvant endocrine therapy preferences in 102 premenopausal women with early-stage breast cancers. Among women having a baseline life expectancy of 5 years, 61% said they would accept endocrine therapy for a 6-month increase in life expectancy and 79% for 1 year; rates were similar if the baseline life expectancy was 15 years. These proportions are close to those for adjuvant chemotherapy found by Duric.

How these estimates correspond to the distant recurrence rates reported in prognostic studies is imprecise, but Henderson (2015) has suggested that below a recurrence threshold of 10% many patients will not elect adjuvant chemotherapy owing to the small absolute benefit. He also noted that a majority of those patients are older with small node-negative tumors. That interpretation is consistent with a recent study of 81 women by Hamelinck et al (2016) who found that 78% of women ages 40 to 49 years, 88% ages 50 to 59, 59% ages 60 to 69, and 40% age 70 or older would accept adjuvant chemotherapy for a 0% to 10% absolute decrease in recurrence risk. There was a wide range of minimally required absolute benefits, with the majority accepting chemotherapy for an absolute benefit of 1% to 5%. At a given age range, fewer women expressed a willingness to accept adjuvant endocrine therapy than chemotherapy for a given mortality benefit.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.
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Policy

BCBSNC may provide coverage for assays of genetic expression as a technique to determine prognosis of breast cancer when determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member’s Benefit Booklet for availability of benefits. Member’s benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Assays of Genetic Expression to Determine Prognosis of Breast Cancer are covered

The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX™) to determine recurrence risk in women with primary breast cancer may be considered medically necessary when the following criteria are met:

1. Patient has early stage (stage 1 or 2) breast cancer; **AND**
2. Oncotype DX™ is the gene expression profile panel used; **AND**
3. The results will aid in the decision for or against chemotherapy; **AND**
4. The patient will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors; **AND**
5. The patient’s breast cancer meets all of the following criteria:
   a) unilateral non-fixed;
   b) estrogen-receptor (ER) positive OR progesterone-receptor (PR) positive;
   c) node-negative (isolated tumor cells and/or micrometastases [less than or equal to 2 mm in size] i.e., pN0(i+) and/or pN1(mi), are not considered positive for the purpose of this guideline);
   d) human epidermal growth factor receptor 2 (HER2)-negative;
   e) tumor size is > 0.5cm; **AND**
6. The gene expression profile is ordered by the physician who will administer the hormonal and chemotherapy, usually the oncologist; **OR,**

    The test is ordered by the treating surgeon after discussing the patient’s clinical situation with the oncologist. The oncologist must have agreed that the patient is a candidate for systemic chemotherapy in addition to hormonal therapy if the Oncotype Dx™ Test result indicates a high risk for recurrence. That discussion must be documented in the patient’s clinical chart.

7. The assay is ordered within 6 months following diagnosis.

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

When Assays of Genetic Expression to Determine Prognosis of Breast Cancer are not covered
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1. All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX®, EndoPredict, the Breast Cancer IndexSM, and Prosigna) are considered investigational. These indications include:
   a. Determination of recurrence risk in invasive breast cancer patients who are lymph node-positive;
   b. Determination of recurrence risk in HER2-positive breast cancers;
   c. Determination of recurrence risk in patients with bilateral invasive disease;
   d. Oncotype DX™ for uses other than described above. (e.g., to predict response to specific chemotherapy regimens).
2. Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery is considered investigational.
3. The use of other gene expression assays (e.g., MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test, the BreastOncPx™, NexCourse® Breast IHC4, or BluePrint®, TargetPrint®, PAM50 Breast Cancer Intrinsic Classifier) is considered investigational for any indication.

Policy Guidelines

Laboratory tests have been developed that detect the expression, via messenger RNA of many 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 postsurgical management of breast cancer or to alter treatment in patients with ductal carcinoma in situ (DCIS), or to recommend extended endocrine therapy in patients who are recurrence-free at 5 years. This report summarizes the evidence of 5 tests: 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 (HER2) status. Studies retrospectively collecting tumor samples from prospective trials that provide 10-year distant recurrence rates or 10-year survival rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the evidence review.

21-Gene Recurrence Score (Oncotype DX®)
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), 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 intervals, 6% to 10%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Breast Cancer Index
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the Breast Cancer Index (BCI), the evidence includes findings from 2 prospective-retrospective studies and 1 registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk BCI score is associated with low 10-year distant recurrence rates. The findings from the registry-based observational study also showed 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.

70-Gene Signature (MammaPrint®)
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 70-gene signature (MammaPrint), the evidence includes a prospective-retrospective study and a study using a cancer registry cohort. 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%). Although the registry study showed a low risk of 10-year distant recurrence, the source is not considered high-quality. A recently reported study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. 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 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 for the study providing CI, 6%). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Early-Stage Node-Positive Invasive Breast Cancer
For decisions on management of early-stage node positive disease, Oncotype DX, EndoPredict, Prosigna and MammaPrint were evaluated. Only studies presenting 10-year distant recurrence rates or 10-year survival rates were included in this part of the evidence review.

21-Gene Assay (Oncotype DX)
For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), the evidence includes two prospective-retrospective studies and a prospective study. The prospective-retrospective studies showed that Oncotype DX stratifies node-positive patients into high and low risk for distant recurrence-free survival. However, only one of the studies reported CIs for estimates and those are very wide. The prospective study included patients with node-negative and node-positive breast cancer. The authors reported that subgroup analyses of patients with node-positive breast cancer who were classified as low risk experienced higher rates of survival than patients classified as high risk, though no rates were provided. There is a wide range of survival improvements over which individual patients would elect or refuse adjuvant chemotherapy, but accurate risk estimates are needed to inform patient decisions. The evidence is insufficient to determine the effects of the technology on health outcomes.

EndoPredict
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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 a study, the 10-year distant recurrence rate in low-risk EPclin score patients was estimated to be 5% (95% CI, 1% to 9%). In the other study, 10-year distant recurrence rate in low-risk EPclin score patients was estimated to be 5%, but the upper bound of the 95% CI was close to 20%. To establish that the test has potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision-making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 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.

Ductal Carcinoma In Situ
The Oncotype DX Breast DCIS Score is the only assay investigated for patients with DCIS. For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS assay, the evidence includes a prospective-retrospective study and a retrospective cohort study. Although 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 Oncotype DX Breast DCIS Score is low enough to consider changing the management of DCIS. The evidence is insufficient to determine the effects of the technology on health outcomes.

Extended Endocrine Therapy
For this indication, Oncotype DX, EndoPredict, BCI, MammaPrint and Prosigna were evaluated. Studies retrospectively collecting tumor samples from prospective trials that provided 10-year distant recurrence rates or 10-year survival rates were included in this part of the evidence review. Studies comparing genetic assays with clinical risk prediction tools were also included.

Oncotype DX (21-Gene Assay)
For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes a study from a previously conducted clinical trial. The study did not show low distant recurrence rates in patients classified as low risk with the test, and no confidence intervals were presented. 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 free of distant recurrence at 5 years considering extending endocrine treatment who receive gene expression profiling with EndoPredict, the evidence includes 1 study of archived tissue samples from a previously conducted clinical trial. The study showed low distant recurrence rates in patients classified as low risk with. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. Additional prospective trials or retrospective-prospective studies of archived samples reporting on the
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association between risk score and survival are needed for confirmation of results from the single study. More importantly, clarity about how the test would inform clinical practice is needed. The evidence is insufficient to determine the effect 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 free of distant recurrence at 5 years who are considering extending tamoxifen treatment who receive gene expression profiling with Prosigna, the evidence includes two 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 would suggest 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 effect of the technology on health outcomes.

**Billing/Coding/Physician Documentation Information**

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 0008M, 0045U, 81519, 81520, 81521, S3854*  
*Providers should not be using 84999 or 88299 to bill for this service now that there is an applicable code.*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

**Scientific Background and Reference Sources**


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Senior Medical Director – 1/2013


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Medical Director review 7/2014


Medical Director review 7/2015.


Medical Director review 12/2016


Medical Director review 4/2018

Policy Implementation/Update Information


6/2/05 References added.

10/8/05 CPT code 88299 added to "Billing/Coding" section.

10/20/05 Added CPT "84999" to "Billing/Coding" section. "84999" and "88299" added to "Policy Key Words" section.

1/5/06 Added 2006 HCPCS code S3854 to "Billing/Coding" section.

5/21/07 Specialty Matched Consultant Advisory Panel review 4/25/2007. No changes to policy statement. Added reference to MammaPrint in "Description" section. Rationale revised under "Policy Guidelines" section. Changed statement in "Billing/Coding" section from "Providers may submit this service using 84999 and 88299" to "Providers should not be using 84999 and 88299 to bill for this service now that there is a specific code." References added.
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2/25/08  Updated policy to change "Policy" statement from "investigational" to "medically necessary because medical criteria and guidelines are met." Criteria added to the "When Covered" section are: "Assays of genetic expression as a technique to determine the risk of recurrence of breast cancer may be considered medically necessary and are eligible for coverage when the following criteria are met. 1. Patient has early stage (stage 1 or 2) breast cancer; AND 2. Oncotype DX™ is the gene expression profile panel used; AND 3. The results will aid the patient in deciding whether or not to undergo adjuvant chemotherapy; AND 4. The patient will be treated with hormonal therapy; AND 5. The patient’s breast cancer meets all of the following criteria: a. unilateral non-fixed; b. estrogen receptor-positive OR progesterone receptor-positive; c. node-negative (isolated tumor cells and/or micrometastases are not considered positive for the purpose of this guideline); d. Her-2 negative; e. tumor size is > 0.5 - 1 cm with moderate/poor differentiation or unfavorable features, OR tumor size > 1 cm. AND 6. In order for coverage to be provided, the gene expression profile must be ordered by the physician that will be administering the hormonal and/or chemotherapy to the patient based on the test results (this will usually be the oncologist). Added the following to the "When Not Covered" section: "1. For indications other than those listed above. 2. HER-2 positive breast cancers. 3. Oncotype DX™ for uses other than described above. (e.g., to predict response to specific chemotherapy regimens) are considered investigational; 4. The use of MammaPrint®, and the Breast Cancer Gene Expression Ratio for any indication is considered investigational."

8/11/08  Added "i.e., pN0(i+) and/or pN1(mi), " to #5.c. under the "When Covered" section. Added "Isolated tumor cells, Macrometastasis, and Micrometastasis" to the "Medical Term Definitions" section.

5/18/09  Revised statement in the Description section to read, "Five gene expression tests are commercially available in the U.S.: Oncotype, MammaPrint, Mammostrat, the Molecular Grade Index, and the Breast Cancer Gene Expression Ratio." Revised Item 4. in the Non Covered section to read, "The use of other gene expression assays (e.g., MammaPrint, Mammostrat, the Molecular Grade Index, and the Breast Cancer Gene Expression Ratio) for any indication is considered investigational." The following statements were added to the Policy Guidelines section: "The June 2007 BCBSA TEC Assessment concluded that the 21-gene RT-PCR assay Oncotype DX™ meets TEC criteria for the following women with node-negative breast cancer: Those receiving aromatase inhibitor-based hormonal therapy instead of tamoxifen therapy, Those receiving anthracycline-based chemotherapy instead of CMF (cyclophosphamide, methotrexate, and 5-FU), Lymph nodes with micrometastases are not considered positive for purposes of treatment recommendations, Those whose tumors are ER-positive or PR-positive. Recent studies show that ER-negative, PR-positive patients also tend to benefit from hormonal therapy." "The Aviara MGISM (molecular grade index) is intended to measure tumor grade using the expression of 5 cell cycle genes and provide prognostic information in ER-positive patients regardless of nodal status. One study evaluated MGI along with Breast Cancer Gene Expression Ratio. Both assays are offered separately and the utility of MGI alone is unclear. "Mammostrat is an IHC test intended to evaluate risk of breast cancer recurrence in postmenopausal, node negative, estrogen receptor-positive breast cancer patients who will receive hormonal therapy and are considering adjuvant chemotherapy." Reference updated. Specialty Matched Consultant Advisory Panel review 4/21/09. (btw)

6/22/10  Policy Number(s) removed. (amw)
Assays of Genetic Expression to Determine Prognosis of Breast Cancer

5/24/11 Specialty Matched Consultant Advisory Panel review 3/30/11. Description section revised. The following statements were added to the “When Covered” section: “The order should be within 6 months following diagnosis, since the value of the test for making decisions when ordered regarding delayed chemotherapy is unknown.” “The 21-gene RT-PCR assay Oncotype DX™ should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should be ordered in the context of a physician-patient discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.” “For patients who otherwise meet the above characteristics but who have multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive 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.” Clarified 5e to read “tumor size is 0.6 - 1cm with moderate/poor differentiation or unfavorable features”. Revised statements in the “When Not Covered” section, no change to policy intent. Updated “Policy Guidelines” section. References added. (btw)


10/16/12 Specialty Matched Consultant Advisory Panel review 3/21/2012. Added the following information to the When Covered section: item 5e. “tumor size is > 0.5cm”. Removed “tumor size is 0.6 - 1cm with moderate/poor differentiation or unfavorable features, OR tumor size > 1cm.” Added the following to item 6. “The test is being ordered by the treating surgeon who has discussed the patient’s clinical situation with the oncologist to whom the patient will be referred, and that oncologist has agreed that the patient IS a candidate for systemic chemotherapy in addition to hormonal therapy if the Oncotype Dx™ Test result indicates a high risk for recurrence. That discussion must be documented in the patient’s clinical chart.” Policy Guidelines section updated. (btw)

2/12/13 Description section revised. In the When Not Covered section added “1.c. Determination of recurrence risk in patients with bilateral disease;“ “2. Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery is considered investigational.” and added NexCourse® Breast IHC4 to the list in number 3. Senior Medical Director review 1/15/13. Reference added. Notification given 2/12/13, policy effective 5/14/2013.(btw)

5/14/13 Specialty Matched Consultant Advisory Panel review March 30, 2013. Removed the following statement from the Policy Guidelines section; “Unfavorable features that may prompt testing in tumors greater than 0.5 cm in size include the following: angiolymphatic invasion, high histologic grade, or high nuclear grade.” (btw)


7/15/14 Description section revised to include updated list of available tests, including Prosigna™. Statement in the “When not Covered” section revised as follows: “The use of other gene expression assays (e.g., MammaPrint® 70-gene signature, Mammastrat® Breast Cancer Test, the Breast Cancer Index SM, the BreastOncPx™, NexCourse®
Assays of Genetic Expression to Determine Prognosis of Breast Cancer

Breast IHC4, or Prosigna™ PAM50 Breast Cancer Intrinsic Classifier) is considered investigational for any indication.” Policy Guidelines updated. References updated. Added new code 0008M to Billing/Coding section. Medical Director review 7/2014. (mco)

1/27/15 Added new CPT code 81519 to Billing/Coding section. (lpr)

4/28/15 Specialty matched consultant advisory panel review meeting 3/25/2015. Under “When Covered” section page 2 item 5c: changed parameters from less than 2mm to less than or equal to 2mm. No change to policy intent. (lpr)

9/1/15 Updated Description and Policy Guidelines sections. Senior medical director review 7/2015. Reference added. (lpr)

12/30/15 Deleted HCPCS code S3854 from Billing/Coding section effective 1/1/2016. (lpr)

4/29/16 Updated Description and Policy Guidelines sections. Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. HCPCS code S3854 added back to the Billing/Coding section until a new code for MammaPrint is approved by CMS. (lpr)

1/27/17 Under When Covered section: added indication that EndoPredict, Prosigna, and Breast Cancer Index are medically necessary for same indication as Oncotype. Revised Policy Guidelines section extensively. Reference added. Medical Director review 12/2016. (lpr)

4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)

10/13/17 Extensive updates to Description and Policy Guidelines sections. Under “When Not Covered” section: removed Prosigna from statement #3 for clarity. No change to policy statement. Reference added. (lpr)

12/29/17 Updated Policy Guidelines section. Added CPT codes 81520 and 81521 to Billing/Coding section. Reference added. No change to policy statement. (lpr)


7/13/18 Added code 0045U to Billing/Coding section effective 7/1/18. (lpr)

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