Assays of Genetic Expression to Determine Prognosis of Breast Cancer

Laboratory tests have been developed that detect the expression, via messenger RNA (mRNA) or protein, 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 post-surgical management.

For women with early-stage breast cancer, (i.e. cancer extends beyond the basement membrane of the milk ducts into adjacent tissue), adjuvant chemotherapy provides the same proportional benefit regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk of recurrence. For example, women with the best prognosis have small tumors, are estrogen receptor positive, and lymph node negative. These women have an approximately 15% baseline risk of recurrence; approximately 85% of these patients would be disease-free at 10 years with tamoxifen treatment alone and could avoid the toxicity of chemotherapy, if they could be accurately identified. Conventional risk classifiers estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. However, no single classifier is considered a gold standard, and several common criteria have qualitative or subjective components that add variability to risk estimates. As a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help women, who prefer to avoid chemotherapy if assured that their risk is low, make better treatment decisions in consultation with their physicians.

Recently, several groups have identified panels of gene expression markers (“signatures”) that appear to predict the baseline risk of breast cancer recurrence after surgery, radiation therapy, and endocrine therapy (for hormone-receptor-positive tumors) in women with node-negative disease. Gene expression tests are commercially available in the United States include:

- Oncotype DX® developed and marketed by Genomic Health Inc. (Redwood City, CA).
- MammaPrint® which is commercially developed by Agendia (the Netherlands; test originally referred to as the 70-gene signature) and was FDA-cleared on February 6, 2007. MammaPrint® is performed in Agendia laboratories in the Netherlands and in California.
- BluePrint® and TargetPrint® is performed in Agendia laboratories.
- Breast Cancer Gene Expression Ratio (also known as the 2-gene ratio or HOXB13/IL-17BR [H/I] index). In 2008, bioMérieux acquired AviaraDx, which is now known as bioTheranostics Inc. (San Diego, CA). bioTheranostics combined the H/I index with a Molecular Grade Index (MGI) to develop the Breast Cancer IndexSM.
- NanoString Technologies Inc. (Seattle, WA) developed and markets the Prosigna™ Breast Cancer Prognostic Gene Signature Assay, which was FDA-cleared on September
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6, 2013. Prosigna™ uses PAM50 (prediction analysis of microarray 50 gene set) for breast cancer subtyping.

- Mammostrat® Breast Cancer Test, developed by Clarient Diagnostic Services, is an IHC assay of 5 biomarkers independent of tumor proliferation and grade.
- BreastOncPx™ (Breast Cancer Prognosis Gene Expression Assay), developed by LabCorp, q is a 14-gene RT-PCR.
- NexCourse® Breast IHC4, developed by Geneoptix, is an IHC assay of ER, PR, HER, and Ki-67.
- BreastPRS™, developed by Signal Genetics, is a 200 gene assay.
- EndoPredict®, developed by Sividon Diagnostics, is a 12-gene real-time RT-PCR.

If these panels are more accurate than current conventional classifiers, they could be used to aid chemotherapy decision-making, when current guidelines do not strongly advocate its use, without negatively affecting disease-free and overall survival (OS) outcomes.

Oncotype DX, using a slightly different algorithm to calculate results, is also marketed for patients with noninvasive, ductal carcinoma in situ (DCIS) to predict the 10-year risk of local recurrence (DCIS or invasive carcinoma). The stated purpose is to help guide treatment decision making in women with DCIS treated by local excision, with or without adjuvant tamoxifilen therapy.

***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.

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;
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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

1. All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX®), EndoPredict, the Breast Cancer Index SM, 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 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 Prosigna™, 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). This report summarizes the evidence of 5 tests for 4 indications and is organized by indication.

For all tests and all indications, relevant outcomes include disease-specific survival and changes in disease status.
Assays of Genetic Expression to Determine Prognosis of Breast Cancer

**Early-Stage Node-Negative Invasive Breast Cancer**
Only studies presenting 10-year distant recurrence rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the evidence review. In addition to negative nodes, the type of patient considered for this indication have positive hormone receptors and are human epidermal growth factor receptor 2 (HER2) negative.

**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, 7%-9%; upper bound of the 95% confidence intervals, 11% to 15%). 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. 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. 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 1 study with outcomes in node-negative patients. Although the study showed a low risk of 10-year distant recurrence in not derived from high-quality data sources. 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. 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 this indication, Oncotype DX and MammaPrint have been evaluated.

**21-Gene Assay (Oncotype DX)**
For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), the
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evidence includes clinical trials and prospective-retrospective studies. Although studies showed that Oncotype DX stratifies node-positive patients into high and low risks, it is still uncertain that the risk of disease recurrence is sufficiently low to avoid chemotherapy. Studies have suggested that treatment benefit in chemotherapy is restricted to high-risk patients. The evidence supporting this treatment interaction should be more robust to consider avoiding otherwise currently recommended treatment in patients not at low risk of recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.

70-Gene Signature (MammaPrint)
For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 70-gene signature (MammaPrint), the evidence includes prospective-retrospective studies. Existing studies have not reported 10-year distant recurrence outcomes in the patients of interest. The studies are confounded by various factors (eg, receipt of treatment) or do not report the outcome of interest. 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 prospective-retrospective studies and prospective trials. 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.

Continuation of Tamoxifen Therapy Beyond 5 Years
For this indication, EndoPredict, BCI, and Prosigna have been evaluated.

EndoPredict
For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen 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 at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.

Breast Cancer Index
For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with BCI, 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 at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect 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 considering extending tamoxifen treatment who receive gene expression profiling with the Prosigna, the evidence includes 2 studies from previously conducted clinical trials. The studies showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of
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extending tamoxifen treatment. 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: 81519, 0008M, 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


Assays of Genetic Expression to Determine Prognosis of Breast Cancer


Senior Medical Director – 1/2013


Medical Director review 7/2014


Medical Director review 7/2015.


Medical Director review 12/2016

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**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.

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 - 1cm with moderate/poor differentiation or unfavorable features, OR tumor size > 1cm. 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.
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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 hormone 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)

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
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candidate for systemic chemotherapy in addition to hormonal therapy if the Oncotype Dxtm 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 Prosinga™. Statement in the “When not Covered” section revised as follows: “The use of other gene expression assays (e.g., MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test, the Breast Cancer Index SM, the BreastOncPx™, NexCourse® Breast IHC4, or Prosinga™ 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, Prosinga, 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)
Assays of Genetic Expression to Determine Prognosis of Breast Cancer

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.