

Corporate Medical Policy

Assays of Genetic Expression to Determine Prognosis of Breast Cancer

File Name:	assays_of_genetic_expression_to_determine_prognosis_of_breast_cancer
Origination:	11/2004
Last CAP Review:	3/2011
Next CAP Review:	3/2012
Last Review:	8/2011

Description of Procedure or Service

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, 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 hormonal therapy (for hormone-receptor-positive tumors) in women with node-negative disease. Five gene expression tests are commercially available in the United States: Oncotype DX™ (a 21-gene reverse transcriptase-polymerase chain reaction [RT-PCR] assay; Genomic Health), the 70-gene signature MammaPrint® (Agendia), Mammostrat® Breast Cancer Test (Clariant Diagnostic Services), the Breast Cancer IndexSM, a combination of the Molecular Grade Index (MGI) and the HOXB13:IL17BR Index (bioTheranostics), the BreastOncPx™ (Breast Cancer Prognosis Gene Expression Assay; LabCorp), and the PAM50 Breast Cancer Intrinsic Classifier (ARUP National Reference Laboratory). 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.

Regulatory Status

All tests except MammaPrint® are provided as laboratory-developed tests (LDTs) in Clinical Laboratory Improvement Act (CLIA)-licensed laboratories operated by each company. These LDTs have not been cleared by the U.S. Food and Drug Administration (FDA); to date, FDA clearance is not required.

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MammaPrint® has received 510(k) clearance for marketing by the FDA. All U.S. tests are performed at the CLIA-licensed Agendia clinical laboratory.

*****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 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 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 0.6 - 1cm with moderate/poor differentiation or unfavorable features, OR tumor size > 1cm. AND
6. The gene expression profile is ordered by the physician who will administer the hormonal and chemotherapy. This will usually be the oncologist.
7. The assay is ordered within 6 months following diagnosis.

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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™) are considered investigational. These indications include:
 - a. Determination of recurrence risk in breast cancer patients who are lymph node-positive;
 - b. Determination of recurrence risk in HER2-positive breast cancers;
 - c. Oncotype DX™ for uses other than described above. (e.g., to predict response to specific chemotherapy regimens).
2. The use of other gene expression assays (e.g., MammaPrint® 70-gene signature, Mammostrat® Breast Cancer Test, the Breast Cancer IndexSM, the BreastOncPx™, or PAM50 Breast Cancer Intrinsic Classifier) for any indication is considered investigational.

Policy Guidelines

21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay “Oncotype DX™”

The 21-gene RT-PCR assay should only be ordered on a tissue specimen obtained during surgical removal of the tumor, 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. The order should be within 6 months following diagnosis, since the value of the test regarding delayed chemotherapy is unknown.

Unfavorable features that may prompt testing in tumors from 0.6 to 1 cm in size include the following: angiolymphatic invasion, high histologic grade, or high nuclear grade.

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.

The “Oncotype DX™” should not be ordered as a substitute for standard estrogen receptor, progesterone receptor, or human epidermal growth factor receptor 2 (HER2) testing.

Other gene expression assays

The Breast Cancer IndexSM is a simultaneous assessment of HOXB13:IL17BR, formerly Aviana H/ISM) and MGISM (Molecular Grade Index, formerly Aviana MGISM). One study evaluated MGI along with H/I; high MGI was associated with significantly worse outcome only in patients with high H/I and vice versa. There are no reclassification studies of comparison with conventional risk classifiers; thus, clinical utility is unclear.

Mammostrat® is an immunohistochemistry (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. A test for an interaction between chemotherapy and the risk group stratification was not significant. There are no published reclassification studies of comparison with conventional risk classifiers.

The TEC Assessment found insufficient evidence to determine whether MammaPrint® or the Breast Cancer Gene Expression Ratio are better than conventional risk assessment tools in predicting the

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recurrence of breast cancer. Recurrence rates in patients classified as low risk in available studies were too high for most to consider forgoing chemotherapy.

Neither the NCCN, nor the American Society of Clinical Oncology specifically support any indications for the use of MammaPrint®, Mammostrat®, Breast Cancer IndexSM, BreastOncPxTM, or PAM50 Breast Cancer Intrinsic Classifier.

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: 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

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.36, 7/15/04

Specialty Matched Consultant Advisory Panel - 4/2005

Paik, S, Shak S, Tang, et al. (2004). A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *New England Journal of Medicine*. 351:2817-26.

BCBSA Technology Evaluation Center. (2005, April). Gene expression profiling for managing breast cancer treatment. Retrieved 5/17/2005 from <http://www.bcbsa.com/tec/tecinpress/04.html>

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.36, 4/1/2005

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.36, 7/20/2006

National Comprehensive Cancer Network Practice Guidelines in Oncology. (2007, January). Breast cancer. Retrieved 2/7/07 from http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf.

Specialty Matched Consultant Advisory Panel - 4/2007

BCBSA Technology Evaluation Center. (2007, September). Gene expression profiling for managing breast cancer treatment. Retrieved 10/25/07 from <http://www.bcbsa.com/betterknowledge/tec/press/gene-expression-profiling-of.html>

Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol*. 2007;25(33) ASCO Special Article.

National Comprehensive Cancer Network Practice Guidelines in Oncology: Breast cancer. (January,

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V,2.2008). Retrieved 1/29/2008 from http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.36, 10/07/08

Specialty Matched Consultant Advisory Panel - 4/2009

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.36, 12/2009

Goldhirsch A, Ingle JN, Gelber RD et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol* 2009; 20(8):1319-29.

Specialty Matched Consultant Advisory Panel – 3/2011

Wolff AC, Hammond ME, Schwartz JN et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 2007; 25(1):118-45.

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.36, 6/9/2011

Policy Implementation/Update Information

- 11/11/04 New policy written. Assays of genetic expression in tumor tissue as a technique to determine prognosis of breast cancer is considered investigational. Notification given 11/11/2004. Effective date of policy 1/20/2005.
- 5/5/05 Specialty Matched Consultant Advisory Panel review 4/14/2005. No changes to criteria. References added.
- 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

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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.
- 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 Aviaira 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

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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)

9/13/11 “Description” section revised. Examples of other gene expression assays updated in the “When Not Covered” section. “Policy Guidelines” section updated. References added. Medical Director review 8/16/2011. (btw)

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.