



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
Policy Number: MED1063
Origination: 11/2004
Last Review: 4/2009
Next Review: 4/2011

Description of Procedure or Service

Currently, prognosis in breast cancer is based on patient age, tumor size, [histology](#), status of the axillary lymph nodes, histologic type, and hormone receptor status. However, patients with the same set of risk factors can have markedly different prognoses. For example, not all patients with larger breast primaries or positive axillary lymph nodes are destined to progress to [metastatic](#) disease, and yet [adjuvant](#) chemotherapy is routinely recommended in all of these patients. A set of more sensitive and specific risk factors would improve patient selection criteria for [adjuvant](#) therapy and other aspects of the treatment of breast cancer.

Recently, there has been interest in examining gene expression in tumor tissue as a [prognostic](#) factor. Five gene expression tests are commercially available in the U.S.: Oncotype DX™, MammaPrint®, Mammostrat™, the Molecular Grade Index, and the Breast Cancer Gene Expression Ratio. These tests measure a specific panel of genes expression markers ("signatures") in the tumor tissue. Patterns of genetic expression can then be compared to outcome databases to identify specific patterns that are associated with prognosis and the likelihood of breast cancer recurrence.

Policy

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

Benefits Application

Please refer to Certificate for availability of benefits. This policy relates only to the services or supplies described herein. Benefits may vary according to benefit design, therefore certificate language should be reviewed before applying the terms of the policy.

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

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** i.e., pN0(i+) and/or pN1(mi), are not considered positive for the purpose of this guideline);
 - d. HER2-negative;
 - e. tumor size is > 0.6 - 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).**

When Assays of Genetic Expression to Determine Prognosis of Breast Cancer is not covered

1. For indications other than those listed above.
2. HER2-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 other gene expression assays (e.g., MammaPrint®, Mammostrat™, the Molecular Grade Index or the Breast Cancer Gene Expression Ratio) for any indication is considered investigational.

Policy Guidelines

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.

Policy: Assays of Genetic Expression to Determine Prognosis of Breast Cancer

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

The Avicara 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.

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 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.

Medical Term Definitions

Adjuvant

assisting or aiding. Something that enhances the effectiveness of a medical treatment.

Histology

a department of anatomy which deals with the minute structure, composition, and function of the tissues.

Isolated tumor cells

are stage pN0(i+) and are deposits of tumor not larger than 0.2 millimeters. (in a lymph node)

Metastatic

transfer of disease from one organ or part of the body to another not directly connected with it.

Macrometastasis

are stage pN1 and are deposits of tumor larger than 2.0 millimeters.

Micrometastasis

are stage pN1(mi) and are deposits of tumor larger than 0.2 millimeters, but not larger than 2.0 millimeters.

Policy: Assays of Genetic Expression to Determine Prognosis of Breast Cancer

Prognostic

prediction of health outcome.

Unfavorable features

angiolymphatic invasion, high nuclear grade, or high histologic grade.

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, 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

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.

Policy: Assays of Genetic Expression to Determine Prognosis of Breast Cancer

- 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.
- 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 Avira 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)

Policy: Assays of Genetic Expression to Determine Prognosis of Breast Cancer

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