



Medical Policy

Subject: Gene Expression Profiling for Managing Breast Cancer Treatment
Policy #: LAB.00014 **Current Effective Date:** 03/09/2007
Status: Reviewed **Last Review Date:** 12/07/2006

Description/Scope

This policy addresses the use of genetic profiling of breast tumors as a technique of predicting breast cancer recurrence and response to therapy.

Policy Statement

Investigational/Not Medically Necessary:

Gene expression profiling as a technique of managing the treatment of breast cancer is considered **investigational/not medically necessary**.

Rationale

Introduction

Validation of gene expression panels to improve risk prediction or treatment outcomes is a multistep process. Genetic test validation in general has been carefully examined in a report funded by the Centers for Disease Control and Prevention. The ACCE (analytic validity, clinical validity, clinical utility and ethical, legal and social implications) Model System for Collecting, Analyzing and Disseminating Information on Genetic Tests (available at <http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm>) provides a framework that is applicable to a variety of genetic tests.

The three sequential steps may be defined as follows: *analytic validity*, in which a panel of candidate genes is identified; *clinical validity* in which preliminary performance studies in relevant populations evaluate the genetic panel association with risk prediction or treatment outcomes; and finally, *clinical utility* in which the results of the multigene assay are actually used to direct the management of the patient. Ideally, clinical utility studies would address the issue of whether the use of the test improves patient outcomes.

There are two general categories of patients that can be considered; 1. patients with node negative breast cancer where the results of the test may be used to determine the risk of recurrence and whether or not additional adjuvant chemotherapy would be of benefit; and 2. patients initiating chemotherapy where the results of the test would be used to predict the optimal chemotherapy regimen. These two categories of patients will be considered separately.

Patients with Node Negative Breast Cancer

There are currently 4 different gene expression profiling assays, in various stages of development, that are intended for eventual use in identifying those patients at low risk of recurrence for whom adjuvant chemotherapy can be avoided. These are the 21-gene Oncotype DX (Genomic Health), the 70-gene

MammaPrint® (Agendia; also referred to as the “Amsterdam signature”), the 76-gene “Rotterdam signature” (Veridex), and a 41-gene signature reported by Ahr, 2001.

Oncotype DX was developed using the candidate gene method: a relatively small number of genes known to be involved in breast cancer progression were selected and by analyzing expression of these genes in tumor specimens, a 21-gene signature predicting recurrence was developed. The other 3 assays were developed by analyzing gene expression of tumor specimens on large scale microarrays with thousands of gene transcripts, followed by pattern or cluster analysis to identify a much smaller gene signature that correlated with disease recurrence. Of these three, two have been compared: a 70-gene panel (MammaPrint® or “Amsterdam signature”) and a 76-gene panel (“Rotterdam signature”) overlap by only 3 genes, due at least partly to the use of different microarray platforms in developing the panels. More recent studies indicate that the 2 panels share 21 biological pathways, if not the same genes. While it is likely that many genes correlate with disease recurrence and survival and different combinations may have equally predictive value, larger numbers of observations than have been reported thus far are needed to validate and arrive at consensus signatures for optimal prediction.

Additionally, because the patient populations used to develop each panel were somewhat different, varying in age distribution, disease state, and race, and the panels themselves are clearly different, it is important to show that all panels accurately predict recurrence outcomes in all relevant populations, or to carefully validate the panel on clearly defined breast cancer subgroups.

All panels were developed using banked specimens from clinical trials or patient cohorts for which long-term patient outcomes were already known. This is an efficient method for defining and establishing the clinical validity of the gene expression signatures. Clinical validity for this application is defined as evidence supporting the ability of the panel to accurately predict outcomes such as disease recurrence, disease-free survival, or overall survival. Evidence of clinical validity has been reported in full-length journal publications for 2 panels, Oncotype DX and MammaPrint®.

No published evidence exists to support the clinical utility of the Oncotype DX or the MammaPrint® assays to exclude women with early stage breast cancer from adjuvant chemotherapy and thereby improve avoidance of unnecessary treatment and side effects while maintaining or improving survival outcomes.

No prospective trials have been conducted in which the Oncotype DX assay is prospectively used to select women with early stage breast cancer for adjuvant chemotherapy. The National Cancer Institute’s Program for the Assessment of Clinical Cancer Tests (PACCT) has proposed a prospective trial in which node-negative, ER-positive breast cancer patients would be assigned hormone therapy only based on a low risk RS.

Regarding MammaPrint®, the translational research network of the Breast International Group (TRANS-BIG) is planning a randomized clinical trial to determine therapy for node-negative cancer patients. In the Microarray for Node Negative Disease may Avoid Chemotherapy Trial (MINDACT), 5000 patients will be randomly assigned to treatment based on conventional histopathological and clinical criteria for recurrence or based on the MammaPrint® 70-gene expression profile.

However, an alternate study design to support clinical utility of Oncotype DX was recently reported in a meeting presentation. Available banked specimens from the randomized tamoxifen + chemotherapy-treated arms of NSABP trial B-20 were compared to the tamoxifen-only arm (samples also used as the test set to develop the assay) and gene expression signatures were correlated to chemotherapy benefit. The 424 selected patients with high RS (>31) had an absolute increase in distant recurrence free survival (DRFS) at 10 years of $17.6 \pm 8\%$ (mean \pm SE; $p=0.01$) compared to the tamoxifen-only group. Patients with low RS (<18) had little benefit from chemo (absolute DRFS increase at 10 years, $-1.1 \pm 2.2\%$). Interaction between chemotherapy and RS was significant at $p<0.05$. These results suggest that Oncotype DX predicts the magnitude of the benefit from chemotherapy, but because they have not been published in full detail, they do not meet the evidence criteria for this Assessment.

Because published evidence supporting clinical utility is not available, the evidence for all of the gene expression panels is insufficient to permit conclusions concerning the effect of gene expression profiling on selecting patients who do not need chemotherapy for the purpose of avoiding adverse outcomes while maintaining or improving disease-free or overall survival outcomes.

Patients with Breast Cancer initiating Therapy

Several studies of gene expression profiling of pretreatment tumor samples to predict response to adjuvant or neoadjuvant chemotherapy regimens have been published or presented at recent meetings. Most studies are first reports of the development of the gene expression signatures from sample test sets. Some include small, within-institution studies of separate validation specimens. Outcomes reported are intermediate measures of response to chemotherapy. No studies link the results of gene expression signatures to disease-free or overall survival outcomes. Thus the evidence is insufficient to permit conclusions regarding the use of gene expression profiling to improve the selection of beneficial chemotherapy regimens and improve disease-free or overall survival outcomes.

Background/Overview

Women with node-negative breast cancer receive on average a small but significant benefit from polychemotherapy administered after primary surgery, with or without hormonal therapy. However, a large proportion of these women would be disease-free at 10 years without systemic therapy or with tamoxifen treatment alone. Thus, only a small proportion actually derives benefit from chemotherapy. However, current algorithms that evaluate tumor stage, histology, size, and receptor status exclude only a small number of women from recommended chemotherapy. A reliable method of identifying those women unlikely to derive benefit from chemotherapy could potentially save many more from the adverse effects of chemotherapy.

Gene expression panels may also improve the prediction of response to various adjuvant and neoadjuvant chemotherapy regimens, helping to select the optimal regimen for individual patients. For example, women with early stage node-negative or node-positive breast cancer may be prescribed neoadjuvant chemotherapy to convert cases of inoperable cancer to operable disease, and to improve disease-free survival. Response, however, to a variety of regimens is not uniform and better methods of predicting response to help select the chemotherapy regimen likely to produce the greatest benefit are needed.

Recently, several groups have identified panels of gene expression markers that appear to predict the likelihood of breast cancer recurrence in various populations of women with node-negative disease. These panels may be useful for identifying those women who are unlikely to experience recurrence and, thus, unlikely to benefit from adjuvant chemotherapy. If validated for clinical utility, such panels could be used to exclude women from adjuvant chemotherapy, thereby eliminating unnecessary treatment and adverse events. One of these gene expression panels, developed and marketed by Genomic Health, Inc., is called Oncotype DX.

Coding

The following codes for treatments and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational/Not Medically Necessary:

CPT

S3854 Gene expression profiling panel for use in the management of breast cancer treatment

ICD-9 Diagnosis

All diagnoses, including:
174.0-174.9 Malignant neoplasm of the female breast
175.0-175.9 Malignant neoplasm of the male breast
233.0 Carcinoma in situ of breast

References

Peer Reviewed Publications:

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3. Ayers M, Symmans WF, Stec J, et al. Gene expression profiles predict complete pathological response to neoadjuvant paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide chemotherapy in breast cancer. *J Clin Oncol.* 2004; 22:2284-2293.
4. Borie N, Bertucci F, Groulet-Martinec A, et al. Gene expression profiling defines new molecular classes and predicts prognosis in breast cancer patients treated with adjuvant chemotherapy: development of a clinical tool to improve management of breast cancer. *Breast Cancer Res Treat.* 2004; 88(Suppl 1):A5035.
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13. Iwao-Koizumi K, Matoba R, Ueno N, et al. Prediction of docetaxel response in human breast cancer by gene expression profiling. *J Clin Oncol.* 2005; 23:422-431.
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15. Klijn JG., Atkins D, Sieuwerts AM, et al. Validation of a 76-gene prognostic profile in clinically relevant subgroups of lymph-node-negative breast cancer patients. *Ann Oncol.* 2004; 15(Suppl 3):A2080. [Abstract].

16. Paik S, Shak S, Tang G, et al. Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients—NSABP studies B-20 and B-14. *Breast Cancer Res Treat.* 2003; 82:A16.
17. Paik S, Shak S, Tang G, et al. A multi-gene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004; 351:2817-2826.
18. Paik S, Shak S, Tang G, et al. Risk classification of breast cancer patients by the Recurrence Score assay: comparison to guidelines based on patient age, tumor size, and tumor grade. *Breast Cancer Res Treat.* 2004; 88(Suppl 1):A104.
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Government Agency, Medical Society, and Other Authoritative Publications:

1. Blue Cross Blue Shield Association. Gene Expression Profiling for Managing Breast Cancer Treatment. TEC Assessment, 2005; 20(3).
2. Hayes Inc. Hayes alert-Technology Assessment Brief. *Gene Expression Profiling of Tumor Tissue to Predict Breast Cancer Recurrence.* Lansdale, PA: Hayes, Inc.: September 2005.

Web Sites for Additional Information

1. National Library of Medicine. Medical Encyclopedia: Breast Cancer. Available at: <http://www.nlm.nih.gov/medlineplus/ency/article/000913.htm>. Accessed on December 5, 2006.

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Oncotype DX®

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Policy History

| Status | Date | Action |
|---------------|-------------|---|
| Reviewed | 12/07/2006 | Medical Policy & Technology Assessment Committee (MPTAC) review. No change to policy position. Updated Rationale and Reference sections. Published on web 03/09/2007. |
| Reviewed | 12/06/2006 | Hematology/Oncology Subcommittee review. No change to policy position. Updated Rationale and Reference sections. |
| Reviewed | 06/08/2006 | MPTAC review. |
| Reviewed | 06/07/2006 | Hematology/Oncology Subcommittee review. Discussion at meeting. No change to policy position. References updated. |
| Reviewed | 12/01/2005 | MPTAC review. |
| Reviewed | 11/30/2005 | Hematology/Oncology Subcommittee review. Discussion at meeting. |

Revised 04/28/2005 No change to policy position.
MPTAC review. Revision based on Policy Harmonization: Pre-merger Anthem and Pre-merger WellPoint.

| Pre-Merger Organizations | Last Review Date | Policy Number | Title |
|---|-------------------------|----------------------|---|
| Anthem, Inc. WellPoint Health Networks, Inc. | 06/24/2004 | 2.11.22 | No previous policy Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer |

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