Genetic Expression Assays for Breast Tumor Tissue
Oncotype DX®/ MammaPrint®

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Table of Contents:  Page:  Cross Reference Policy:

POLICY DESCRIPTION  2  Genetic Testing, 2016M0038C
COVERAGE RATIONALE/CLINICAL CONSIDERATIONS  2  Comparative Genomic Hybridization Microarray Testing, 2014M0013B
BACKGROUND  4  Genetic Counseling, 2015M0039A
REGULATORY STATUS  8  Chemosensitivity And Chemoresistance Assays In Cancer, 2015M0024A
CLINICAL EVIDENCE  11
APPLICABLE CODES  12
REFERENCES  12
POLICY HISTORY/REVISION INFORMATION  16

INSTRUCTIONS:
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POLICY DESCRIPTION:

This document addresses the use of genetic profiling of breast tumors as a technique of predicting breast cancer recurrence and response to chemotherapy in women with early stage breast cancer.

The test is performed after surgery and the results will assist in determining overall survival, recurrence probability of the tumor, appropriate treatment options, and decisions regarding chemotherapy. Used in conjunction with other clinical tests and risk assessments, gene profiling assays help identify women who do not need adjuvant chemotherapy.

COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:

Oncotype Dx® Gene Expression Assay:
Gene expression profiling with the Oncotype Dx® serum tumor marker test (21-genes RT-PCR assay) as a technique to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy, is considered MEDICALLY NECESSARY for managing the treatment in females or males with recently diagnosed breast cancer. All of the following criteria must be met:

1. Surgery and full pathological evaluation of the specimen has been completed.
2. Breast tumor is stage 1 or stage 2.
3. Axillary-node negative or has axillary-node micrometastasis 2.0 millimeters, or less, in size in one or more lymph nodes (as determined by a sentinel lymph node biopsy and/or axillary dissection).
   
   Note: See Tumor Classification table in the Attachment Section.
4. There is no evidence of distant metastatic breast cancer.
5. Breast tumor is:
   a. Estrogen receptor positive (ER+), or progesterone receptor positive (PR+), or both
   b. Human epidural growth factor receptor 2 (HER2) receptor negative
6. The individual is a candidate for possible adjuvant chemotherapy.
7. The patient will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors.
8. The member and physician (prior to testing) have discussed the potential results of the test, which will help to decide for or against chemotherapy.
9. Test ordered within 6 months of primary breast cancer diagnosis.

MammaPrint® Gene Expression Assay:
Gene expression profiling with the MammaPrint® (70-genes from tumor samples that are fresh frozen) as a technique to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy, is considered MEDICALLY NECESSARY for managing the treatment in females or males with recently diagnosed breast cancer. All of the following criteria must be met:

1. Surgery and full pathological evaluation of the specimen has been completed.
2. Breast tumor is stage 1 or stage 2.
3. Tumor size less than or equal to 5.0 cm.
4. Axillary-node negative (as determined by a sentinel lymph node biopsy and/or axillary dissection).
5. There is no evidence of distant metastatic breast cancer.
6. Breast tumor is:
   a. Estrogen receptor positive (ER+/−), or progesterone receptor positive (PR+), or both
   b. Human epidermal growth factor receptor 2 (HER2) receptor negative
7. The individual is a candidate for possible adjuvant chemotherapy.
8. The patient will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors.
9. The member and physician (prior to testing) have discussed the potential results of the test, which will help to decide for or against chemotherapy.
10. Test ordered within 6 months of primary breast cancer diagnosis.

**Note:** MammaPrint® assay uses fresh frozen tissue and in 2015 was FDA approved in formalin-fixed paraffin-embedded tissue samples. However, only one published study describing the analytical validity of the commercially marketed MammaPrint® test using formalin-fixed paraffin-embedded (FFPE) tissue samples was identified; therefore, analytical validity of that application is **INVESTIGATIONAL** due to insufficient clinical evidence of safety and/or efficacy in published, peer-reviewed medical literature.

### Multiple Primary Breast Tumors:
Oncotype DX® or MammaPrint® may be considered **MEDICALLY NECESSARY** if each primary breast tumor separately meets the criteria listed above. If multiple breast tumors meet the eligibility criteria, the Recurrence Score (RS) from one tumor must be determined before subsequent testing of another tumor.

Oncotype DX® or MammaPrint® gene expression assay may be considered **MEDICALLY NECESSARY** for predicting breast cancer recurrence for multiple primary breast tumors, when all of the following criteria are met:

1. Each primary breast tumor MUST separately meet the criteria above for Oncotype DX or MammaPrint.
2. If both breast tumors meet criteria for testing, the Recurrence Score (RS) (e.g., test results) from one tumor must be known before testing another tumor.

   **Note:** If Recurrence Score (RS) on the first tumor is high, then testing on a subsequent tumor is unnecessary. If RS on the first tumor is intermediate or low, then testing on a subsequent tumor may be considered.

### EXPERIMENTAL/INVESTIGATIONAL:
Because inadequate clinical evidence of safety and/or efficacy in published, peer-reviewed medical literature that demonstrates the test improves health outcomes, all other applications for gene expression profiling with the Oncotype Dx® or MammaPrint® are considered **EXPERIMENTAL/INVESTIGATIONAL** and therefore, not covered, including but not limited to:

1. Determination of recurrence risk in breast cancer patients with positive lymph nodes.
2. When more than six months have elapsed since initial diagnosis of breast cancer (the Oncotype Dx® role relative to delayed adjuvant chemotherapy has not been established).
3. Other clinical indications for the Oncotype Dx®, including its use for predicting the likelihood of disease recurrence for patients with ductal carcinoma in situ (DCIS) and stage II colon cancer following surgery.

The use of other gene expression profiling assays for any indication in tumor tissue, is considered
### EXPERIMENTAL/INVESTIGATIONAL

and therefore, not covered, including but not limited to:

1. Breast Cancer Gene Expression Ratio (also known as Theros H/ISM)
2. HERmark® Breast Cancer Assay
3. Insight® DX Breast Cancer Profile
4. The 76-gene "Rotterdam signature" assay
5. The 41-gene signature assay
6. Mammostrat®
7. THEROS Breast Cancer IndexSM
8. Oncotype Dx® DCIS

The safety and/or efficacy of these services cannot be established by review of the available published, peer-reviewed medical literature.

### Clinical Considerations:

The Oncotype DX® or MammaPrint® should only be ordered after surgery, subsequent pathology examination, receptor status of the breast tumor has been completed, and the test result will aid in making decisions regarding chemotherapy. The ordering health care professional's documentation should indicate the following:

- The individual has cancer of the breast that is hormone receptor-positive and node-negative.
- The member is a candidate for adjuvant chemotherapy and he/she is not precluded due to significant co-morbidities and/or any other factor.
- The intention to treat or not treat with adjuvant chemotherapy would be contingent, at least in part, on the results of the test for the individual in question and would play a significant role in management of the individual.

The Oncotype Dx® or MammaPrint® assay test should not be run until receptor status is known. The receptor is run by Genomic Health, and if negative, the test is not done and there is no charge for the re-measurement.

### Role of Genetic Counseling:

The role of genetic counseling is limited as there are no known consequences for family members. Results of a psychosocial study of MINDACT participants suggest, however, that additional psychological counseling and support may reduce the distress associated with the results of genetic testing, particularly in patients with high recurrence risk or discordant clinical and genetic risk designations.

### BACKGROUND:

Breast cancer is the most commonly diagnosed malignant tumor and the second leading cause of cancer deaths among women in the United States. It is estimated that more than 220,000 new cases are identified in the US every year, which lead to approximately 40,000 deaths annually. While common, breast cancer is highly treatable when identified early and has a 98.4% 5-year survival rate. However, once spread to the lymph nodes (disease is node positive, or N+); the 5-year survival rate drops to 83.6% and to 23.8% if the cancer has metastasized.

Commonly used prognostic factors that are used to help guide administration of adjuvant chemotherapy are: age; menopausal status; cancer stage and location; histologic and nuclear tumor grade; estrogen (ER),
progesterone (PR), and HER2 (ERBB2) receptor status; and measures of proliferation of the tumor. Because of the complexity of making these decisions, several guidelines and prognostic models are used to identify patients at high risk for disease-specific mortality or greater chance of recurrence. The Oncotype DX assay has been developed to predict which women are at greater risk of recurrence of invasive breast cancer and are therefore more likely to benefit from treatment with adjuvant chemotherapy.

The continuum of breast cancer care begins with regular screening, and continues with timely follow-up and appropriate treatment. If the patient is suspect for breast cancer, needle aspiration and/or a biopsy may be performed. Tissue obtained from a biopsy may be tested by a hormone receptor assay to determine the presence or absence of positive or negative estrogen and progesterone receptors, and for the presence of the human epidermal growth factor receptor 2, also called HER2/neu. Breast tumors are also staged according to tumor size (T), lymph node involvement (N) and metastasis (M).

Men can also acquire breast cancer, and the pathology is similar to females. Prognostics factors in men include the size of the tumor and lymph node involvement. The American Cancer Society (ACS) and the National Cancer Institute (NCI) recommend testing for estrogen- and progesterone-receptor status in men. A small number of breast cancers in men may express the HER2/neu protein.

The selection of individuals with breast cancer who may be candidates for chemotherapy is a complex and inexact science at this time. The current tools available for recurrence risk assessment are limited and do not allow for great accuracy in the selection of appropriate individuals who would and would not benefit from treatment with chemotherapeutic agents. More precise identification of these individuals could improve health outcomes through more appropriate chemotherapy use, mitigation of unnecessary treatment, and decreased adverse chemotherapy-related events.

Assays of genetic expression, gene expression analyses, or gene-expression profiling have been proposed as an adjuvant tool to assist in determining overall survival, recurrence probability, appropriate treatment options, and responsiveness to chemotherapy. Used in conjunction with consensus guidelines and risk assessments, gene profiling assays may help to identify those women who do not need adjuvant chemotherapy. Several panels of gene expression tests (“signatures”) that appear to predict the baseline risk of breast cancer recurrence after surgery, radiation therapy, and endocrine therapy (for hormone receptor-positive tumors) are commercially available in the United States.

1. **21-gene Oncotype Dx®**: It is a patented gene panel laboratory-test, also known as the 21-gene, reverse-transcriptase polymerase chain reaction (21-gene RT-PCR) assay, performed at Genomic Health Laboratories. The assay can be conducted on routine paraffin-embedded breast cancer tissue. It analyzes the expression of a panel of 21 genes and quantifies a Recurrence Score (RS) that is used to identify the likelihood of breast cancer recurrence in women with newly diagnosed stage I or II, node negative, estrogen receptor positive breast cancer, who will be treated with tamoxifen. It is intended for use in conjunction with other conventional methods of breast cancer analysis. Together with staging, grading, and other tumor marker analyses, Oncotype Dx® provides a greater insight as a prognostic tool to quantify the likelihood for disease-free survival at 10 years. For any RS, the likelihood of recurrence is greater with positive nodes than for negative nodes, and it is greater for 4 or more positive nodes than for 1-3 positive nodes.

2. **The 70-gene MammaPrint®**: This test is also referred to as the "Amsterdam signature" (Agendia, BV, Amsterdam, Holland): It is a deoxyribonucleic acid (DNA), in-vitro microarray diagnostic test that uses gene expression profiling to analyze the gene activity of the breast cancer tumor. MammaPrint® allows
for more accurate prognosis of breast cancer recurrence and may help physicians treat breast cancer. MammaPrint® helps identify tumors as high or low risk for recurrence, which may reduce unnecessary chemotherapy and its inherent risk. MammaPrint assay uses fresh frozen tumor tissue for prediction of risk of breast cancer recurrence in women with primary breast cancer. No published studies describe the analytical validity of the commercially marketed MammaPrint® test using formalin-fixed paraffin-embedded (FFPE) tissue samples; therefore, analytical validity of that application is investigational.

Only one published study of the analytical validity of the commercially marketed MammaPrint® test using formalin-fixed paraffin-embedded (FFPE) tissue samples was identified. Sapino et al. (2014) studied laboratory procedures for enabling the MammaPrint assay to be run on formalin-fixed, paraffin-embedded tissue (FFPE) were determined using 157 samples as the technical cohort. An additional set of 125 FFPE samples with matching fresh tissues was used as the establishment cohort for calibration of the MammaPrint-FFPE read-out. A third cohort, an independent equivalence cohort of 211 FFPE samples (from 5 hospitals) with matching fresh tissue samples was used to validate the FFPE analyte test. Reproducibility, repeatability, and precision of the FFPE assay (n = 87) was established for duplicate analysis of the same tumor, interlaboratory performance, 20-day repeat experiments, and repeated analyses over 12 months. FFPE sample processing had a success rate of 97%. The MammaPrint assay using FFPE analyte demonstrated an overall equivalence of 91.5% (95% confidence interval, 86.9% to 94.5%) between the 211 independent matched FFPE and fresh tumor samples. Precision was 97.3%, and repeatability was 97.8%, with highly reproducible results between replicate samples of the same tumor and between two laboratories (concordance, 96%). Thus, with 580 tumor samples, MammaPrint was successfully translated to FFPE tissue. The authors concluded the assay has high precision and reproducibility, and FFPE results are substantially equivalent to results derived from fresh tissue.

3. Mammostrat® Breast Cancer Test (Clarien Diagnostic Services): It is an immunohistochemistry (IHC) test used to evaluate the risk of breast cancer recurrence in individuals with postmenopausal, node-negative, ER-positive breast cancer, who will receive hormonal therapy and are considering adjunctive chemotherapy. Peer-reviewed published literature does not establish the efficacy or clinical utility of this other gene expression assay.

4. Rotterdam Signature 76-Gene Panel: The Rotterdam Signature 76-gene panel was developed to assist physicians to predict the likelihood that a patient with early-stage breast cancer will develop a metastasis. The microarray assay represents a prognostic molecular marker that is proposed to be used with all lymph node negative (LNN) breast cancer patients, regardless of age, tumor size and grade, or ER status. Sixty genes evaluate ER-positive samples and 16 genes evaluate ER-negative samples. The 76-gene signature analyzes fresh-frozen tumor samples and classifies patients as having a gene expression signature associated with either a low or high risk of developing metastatic disease. The test is not yet commercially available.

5. BluePrint™ Molecular Subtyping Profile (Agendia, Irvine, CA): It is an 80-gene assay proposed to classify breast cancer into basal-type, luminal-type or ERBB2-type (HER2/neu positive) cancers. These cancers may have various prognosis and treatment responses to endocrine or chemotherapy based on their molecular subtype. BluePrint™ is proposed to be used in conjunction with MammaPrint® to predict which patients will benefit from endocrine therapy and which will benefit from chemotherapy (Agendia, 2011; Krijgsman, et al., 2011).

6. Breast Bioclassifier™ (AURA, Salt Lake City, UT): It is a 55-gene RT-PCR assay that classifies ER-positive
and ER-negative breast cancers to help predict outcomes. The test provides biologic subtypes of breast cancer and reports outcomes as a continuous risk score.

7. **Breast Cancer Gene Expression Prognosis Profile (BreastOncPx™):** BreastOncPx™ is a 14-gene signature proposed for use in lymph node negative, ER-positive patients to estimate the likelihood of recurrence, including distant metastasis (Laboratory Corporation of America, 2010). Tutt et al. (2008) reported that the sensitivity and specificity of the metastasis score (MS) high and low risk groups to predict distant metastases were 96% and 43% at five years, respectively, and 93% and 46% at ten years, respectively. Sensitivity and specificity of the MS risk groups to predict death from any cause at 10 years were 84% and 45%, respectively.

8. **The THEROS Breast Cancer Molecular Grade Index** (Aviara MGI™ offered by Aviara DX, Inc): This Index has been marketed for predictive risk assessment as well. At this time there are no peer-reviewed published studies describing this test and its possible impact on clinical outcomes.

9. **The Breast Cancer Index™** (bioTheranostics, SanDiego, CA): It is a combination of the Theros H/I (HOXB13:IL17BR, formerly Aviara™ H/I) and the bioTheros MGI™ (Molecular Grade Index, formerly Aviara MGI™). The Theros H/I is a two-gene index that stratifies ER-positive cancer for endocrine therapy benefit. The Theros MGI is a five-gene index that provides quantitative and objective molecular assessment of tumor grade and proliferative rate. MGI discriminates between tumor grades 1 and 3 and reclassifies grade 2 tumors into low- or high-risk. It is also a prognostic indicator for ER-positive patients regardless of nodal status and indicative response to chemotherapy. Each test stratifies breast cancers as low or high for recurrence. It is proposed that by combining these two individual test results, one would obtain independent and complementary prognostic information. Results using the combined testing are reported as low-, intermediate- or high-risk for recurrence. The H/I and the MGI tests can be used independently. bioTheranostics is a CLIA-certified laboratory (bioTheranostics, 2011).

10. **The PAM50 Breast Cancer Intrinsic Classifier** (ARUP National Reference Laboratory, Salt Lake City, UT): PAM50 is a qRT-PCR assay that measures the expression of 50 classifier genes and five control genes to identify four breast cancer tumor subtypes (i.e., luminal A, luminal B, HER2-enriched, basal-like). The test is recommended for patients with invasive breast cancer, regardless of the stage or ER status to aid in determining treatment strategies (ARUP, 2011). According to Nielsen et al. (2010) the “PAM50 qRT-PCR data allow detailed quantitative assessment of the functionality of the estrogen response pathway (8-gene luminal signature) as well as a proliferation signature based on the mean expression of 11 genes linked to cell cycle. The availability of all these measurements provides an opportunity to determine which approach most accurately captures the prognostic effect of estrogen pathway biomarkers and tumor growth rate in a direct comparison.”

11. **The Randox Assay** (BCA) (Randox Laboratories Limited, United Kingdoms): It is a complementary DNA (cDNA)-based expression biochip assay that is proposed to define clinical sub-types of breast cancer tumors prior to initiating treatment. The target population includes all individuals with a diagnosis of breast cancer.

12. **TargetPrint®** (Agendia, Irvine, CA): It is a microarray for the quantitative assessment of ER, PR and HER2 levels. This diagnostic test measures the expression of ER, PR and HER2 genes at the messenger RNA (mRNA) level compared to the expression of the proteins encoded by the genes as determined by immunohistochemistry (IHC). The test is proposed to be used in conjunction with MammaPrint®.
13. **HERmark® Breast Cancer Assay** (Monogram Biosciences, South San Francisco, CA): It is a dimerization assay proposed to quantitatively measure HER2 total protein (H2T) and functional HER2 homodimers (H2D) to aid in stratifying patients with breast cancer who are likely to respond to trastuzumab (Herceptin®)-containing therapy. The test uses two monoclonal antibodies specific for epitopes on the HER2 receptor, which results in both antibodies binding to the same HER2 receptor.

**Other Assays:** Additional gene-profiling assays under investigation include the following:

14. **eXagenBC™** (eXagen Diagnostics, Inc., Albuquerque, NM): is a fluorescence in situ hybridization (FISH) assay proposed for assessing breast cancer metastases in women with newly diagnosed, early stage invasive ductal breast cancer. The test has been submitted for FDA approval and is currently only available in investigational use.

15. **Invasiveness Signature™** (Oncomed Pharmaceuticals, Redwood City, CA): is a test consisting of 186 genes and is designed for node negative, node positive, ER-negative and ER-positive breast cancers.

16. **NuvoSelect™ eRx** (Nuvera Bioscience, Inc., Woburn, MA): it is a 200-gene diagnostic assay to help determine the appropriate treatment for breast cancer patients. It is proposed to predict response to endocrine therapy.

17. **NuvoSelect cRx** (Nuvera Bioscience, Inc., Woburn, MA): A 207-gene predictor that is proposed to predict taxane-based chemotherapy response (Nuvera Biosciences, 2011; Ross, 2008; Liu, et al., 2007).

**REGULATORY STATUS:**

1. **U.S. FOOD AND DRUG ADMINISTRATION (FDA):**
   
   Assays of genetic expression in tumor tissue are specialized tests performed at a limited number of reference laboratories and do not, to date, require FDA marketing clearance. However, Clinical Laboratory Improvement Amendments (CLIA) establish quality standards for all laboratory testing. 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).

   In February 2007, the FDA approved the first molecular prognostic test, MammaPrint® (Agendia BF, Amsterdam, The Netherlands), “a qualitative in vitro diagnostic test, performed in a central laboratory, using the gene expression profile of fresh breast cancer tissue samples to assess a patient’s risk for distant metastasis (up to 10 years for patients less than 61 years old, up to 5 years for patients ≥ 61 years)”. Per the FDA approval, “the test is performed for breast cancer patients, with Stage I or Stage II disease, with tumor size ≤ 5.0 centimeters (cm) and who are lymph-node negative. The MammaPrint® result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors” (FDA, 2011; FDA, Feb 2007). The FDA did not require prospective clinical trials for the approval.

   MammaPrint FFPE received FDA 510(k) K141142 on 23-Jan-15.

   “MammaPrint® FFPE is a qualitative in vitro diagnostic test, performed in a central laboratory, using the gene expression profile obtained from formalin-fixed paraffin embedded (FFPE) breast cancer tissue samples to assess a patient’s risk for distant metastasis within 5 years.
The test is performed for breast cancer patients, with Stage I or Stage II disease, with tumor size ≤ 5.0 cm and lymph node negative. The MammaPrint® FFPE result is indicated for use by physicians as a prognostic marker only, along with other clinico-pathological factors.”

2. **CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):**

Medicare does not have a National Coverage Determination (NCD) regarding Gene expression profiling as a technique of managing the treatment of breast cancer.

**Local Coverage Determinations (LCDs) and local Articles:**
Minnesota/Wisconsin region does not have a LCD that addresses Oncotype Dx®. However, gene expression profiling for managing the treatment of breast cancer, is addressed in other geographic jurisdictions.

The application of gene expression profiling using Oncotype Dx® is employed to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. A Recurrence Score™ (RS) is calculated from the gene expression results using a proprietary Oncotype Dx® algorithm, which is then used to assign a patient to one of three groups by estimated risk of distant recurrence: low, intermediate and high. Patients with high recurrence scores (RS) appear to achieve relatively more benefit from adjuvant chemotherapy.

**INDICATIONS:**
Medicare will consider the application of gene expression profiling using Oncotype Dx® as medically reasonable and necessary, with case by case review as needed, when used to assess the need for adjuvant chemotherapy in patients with recently diagnosed breast cancer (six months or less have elapsed) when all of the following criteria are met:

- Breast cancer is nonmetastatic (node-negative) (lymph nodes with micrometastases are not considered positive); and
- Breast cancer is unilateral and non-fixed (i.e., tumor not adhered to chest wall); and
- Breast tumor is hormone receptor-positive (estrogen receptor (ER)-positive or progesterone receptor (PR)-positive); and
- Breast tumor is HER2-receptor negative; and
- Breast tumor size is 0.6-1 cm with moderate/poor differentiation or unfavorable features (e.g., angiolymphatic invasion, high nuclear grade, or high histologic grade), **OR** tumor size is >1 cm; and
- Breast tumor is stage 1 or stage II; and
- Breast cancer will be treated with hormonal therapy; and
- Adjuvant chemotherapy is not precluded due to any other factor (e.g., advanced age and/or significant co-morbidities); and
- Testing is being done specifically to guide the decision as to whether or not adjuvant chemotherapy will be used and, prior to testing the patient and oncologist have discussed the potential results of the test and agree to use the results to guide therapy (i.e., the patient will forgo adjuvant chemotherapy if Oncotype Dx® score is low).

Medical tests are covered only when ordered by the treating oncologist, when necessary for diagnosis or treatment decisions, and when used in patient care (42 CFR 410.32).

**LIMITATIONS:**
All other uses of Oncotype Dx® are considered experimental or investigational; specifically, the...
following indications:

- To predict response to specific chemotherapy regimens
- Repeat Oncotype Dx® testing or testing of multiple tumor sites in the same patient

In a clinical trial, this test would typically be used for data collection and would not be considered a routine cost and, therefore, this service would not be billed.

Gene expression profiling as a technique of managing the treatment of breast cancer is considered investigational and not medically necessary when a gene profiling test other than the Oncotype Dx® breast cancer assay is used, including but not limited to:

- Breast Cancer Gene Expression Ratio
- MammaPrint®
- Rotterdam 76-Gene Signature
- The 41-gene signature assay
- Amsterdam 70-Gene Profile

**DOCUMENTATIONS REQUIREMENTS:**

The following documentation should be available for review upon request:

- Patient history and physical; and
- Pathology report; and
- Documentation which indicates all of the following:
  a. The results of the Oncotype Dx® test are expected to play a significant role in management of the patient; and
  b. The patient is a candidate for possible adjuvant chemotherapy (i.e., chemotherapy is not precluded due to other factors) and testing is being done specifically to guide the decision as to whether or not adjuvant chemotherapy will be used; and
  c. The genomic information derived from this test has been integrated with copathological parameters, such as patient age and functional status, comorbidities and tumor grade.

Oncotype Dx® should only be ordered after surgery and subsequent pathological examination of the tumor have been completed. The test should be ordered in the context of a physician-patient discussion regarding risk preferences and when the test result will aid the patient in making decisions regarding chemotherapy.

**3. MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):**

Minnesota DHS has coverage criteria regarding Gene expression profiling as a technique of managing the treatment of breast cancer in its Provider Manual. Oncotype Dx testing is a 21 gene assay test, which aims to help breast cancer patients and their physicians determine whether adjuvant chemotherapy would be beneficial. For dates of service January 1, 2012, forward testing is considered medically indicated for recipients with the following breast cancer characteristic:

- Stage I or II breast cancer; and
- Breast tumor is estrogen-receptor positive; and
- Breast tumor is HER2-receptor negative; and
- Tumor size 0.6-1 cm with moderate/poor differentiation or unfavorable features, or tumor size >1 cm
cm;
- Negative lymph nodes (nodes with micrometastases > 2 mm in size); and
- Test result will be used to guide decision making about adjuvant chemotherapy.

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<th>CLINICAL EVIDENCE:</th>
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<tr>
<td>1. SUMMARY</td>
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<tr>
<td>Oncotype DX®:</td>
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<td>Despite the lack of evidence of clinical utility from randomized controlled trials, Oncotype DX® scoring has become an accepted standard of care when evaluating patients without lymph node involvement. When used as a complementary decision-making tool, in combination with other clinical indicators (e.g., tumor size and grade, hormone receptor status, HER2 status), Oncotype Dx® may provide clinical utility to determine whether or not a specific subset of woman with low-risk indicators might benefit from adjuvant chemotherapy. Oncotype Dx® is not indicated as a stand-alone test to be solely relied upon for withholding chemotherapy, nor is it indicated for use in high-risk or intermediate-risk patients (e.g., human epidermal growth factor receptor 2 [HER2]-positive or ER-negative). There is no evidence from randomized controlled trials (RCTs) demonstrating clinical utility of Oncotype DX® testing in the node-positive population. In addition, the use of this assay in node-positive breast cancer patients is not supported by strong evidence of clinical validity comparable to the evidence available for node-negative patients. For women with node-positive breast cancer, it is less clear that the risk of recurrence in low-risk RS patients is sufficiently low, or that the benefit of chemotherapy is insufficiently large, to recommend avoiding otherwise currently recommended treatment. In addition, NCCN guidelines note that patient selection for assay use in lymph node-positive patients remains controversial. Additional studies of Oncotype DX® in lymph node-positive patients are necessary and ongoing. Therefore, Oncotype DX® testing in node-positive patients is considered investigational.</td>
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<td>MammaPrint®:</td>
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<td>A large number of studies of clinical validity, and a few attempting to address the clinical utility of the MammaPrint® (70-gene signature) have been published. Several studies have pooled and re-analyzed subsets of previously published data in attempts to arrive at more homogeneous sample populations. Nevertheless, the studies of the 70-gene signature continue to suffer from confounding in heterogeneous sample populations. Pooled re-analyses of subpopulations may control for one variable (e.g. nodal status), but confounding remains from other variables (e.g. treatment heterogeneity). Results for the 70-gene signature good prognosis patients have confidence intervals that extend into ranges that likely confer too much risk for patients and providers in the U.S. Because the test result is not a continuous numerical value, patients cannot view their result within the spectrum of good prognosis results and adjust their preferences accordingly. Therefore, MammaPrint® testing is considered investigational.</td>
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<tr>
<td>Other Tests:</td>
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<tr>
<td>The available evidence supporting the THEROS Breast Cancer Index®, Molecular Grade Index (Aviara MGI®), Mammostrat®, BreastOncPx™, Breast Cancer Gene Expression Ratio, HERmark® Breast Cancer</td>
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Assay, Rotterdam Signature 76-Panel. And PAM50 Breast Cancer Intrinsic Classifier tests is limited in quantity and quality. No clear and reliable evidence supporting clinical utility is available for these tests. Studies have primarily been in the form of retrospective validation with small heterogeneous patient populations and short-term follow-ups. In addition, neither the National Comprehensive Cancer Network (NCCN) nor the American Society of Clinical Oncology (ASCO) guidelines currently recommend these tests as an option when evaluating breast cancer patients for risk of recurrence. Therefore, THEROS Breast Cancer Index™, Molecular Grade Index (Aviara MGI™), Mammostrat®, BreastOncPx™, and PAM50 Breast Cancer Intrinsic Classifier tests are considered investigational.

Supporting data on the use of gene expression assays in men are lacking.

**APPLICABLE CODES:**

*The Current Procedural Terminology (CPT®) codes and HCPCS codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.*

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<th>HCPCS Codes</th>
<th>Description</th>
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<tr>
<td>S3854</td>
<td>Gene expression profiling panel for use in the management of breast cancer treatment</td>
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<thead>
<tr>
<th>ICD-9-CM Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>174.0-174.9</td>
<td>Malignant neoplasm of female breast</td>
</tr>
<tr>
<td>175.0-175.9</td>
<td>Malignant neoplasm of male breast</td>
</tr>
<tr>
<td>233.0</td>
<td>Carcinoma in situ of breast</td>
</tr>
<tr>
<td>V10.3</td>
<td>Personal history of malignant neoplasm, breast</td>
</tr>
<tr>
<td>V86.0</td>
<td>Estrogen receptor positive status (ER+)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C50.011-C50.929</td>
<td>Malignant neoplasm of breast</td>
</tr>
<tr>
<td>C79.81</td>
<td>Secondary malignant neoplasm of breast</td>
</tr>
<tr>
<td>D05.00-D05.02</td>
<td>Lobular carcinoma in situ of breast</td>
</tr>
<tr>
<td>D05.80-D05.92</td>
<td>Other and unspecified type of carcinoma in situ of breast</td>
</tr>
<tr>
<td>Z17.0</td>
<td>Estrogen receptor positive status [ER+]</td>
</tr>
<tr>
<td>Z85.3</td>
<td>Personal history of malignant neoplasm of breast</td>
</tr>
</tbody>
</table>

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**REFERENCES:**


### POLICY HISTORY:

<table>
<thead>
<tr>
<th>DATE</th>
<th>ACTION/DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-24-2013</td>
<td>Reviewed and approved by the Quality Improvement Advisory and Credentialing Council (QIACC).</td>
</tr>
<tr>
<td>01-30-2013</td>
<td>Approved by the Interim Medical Policy Committee (IMPC).</td>
</tr>
<tr>
<td>11-22-2013</td>
<td>Published to UCare.org</td>
</tr>
</tbody>
</table>
| 03-01-2014 | Annual Review:  
• Policy Number has changed to 2014M0008B.  
• Policy Title has changed to Oncotype DX®/ MammaPrint® Genetic Expression Assays for Breast Tumor Tissue.  
• Revised Coverage Rationale: MammaPrint® gene expression assay Investigational status was changed to Medically Necessary technique to determine recurrence risk for breast cancer.  
• Updated Background, Clinical Evidence, and References sections.  
• Updated Coding section to include ICD-10 codes. |
| 03/12/2014 | New Policy. Reviewed by Medical Policy Committee.                                                                                               |
| 03/27/2014 | Reviewed and approved by the Quality Improvement Advisory and Credentialing Committee (QIACC).                                                   |
| 01/09/2016 | Policy updated. Reviewed and approved by Medical Policy Committee.  
• Policy number changed to 2016M0008B.                                                                                                           |
| 01/28/2016 | Reviewed and approved by the Quality Improvement Advisory and Credentialing Committee (QIACC).                                                   |
| 02/01/2016 | Published to ucare.org                                                                                                                          |

### ATTACHMENTS:

**TNM (tumor size, nodal involvement, and metastasis) classification:**

Classification system used for characterizing the size and location of breast cancer. The system is described below (Note: A prefix of “p” indicates by pathology report):

**Primary Tumor:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no associated tumor. Note: Paget's disease associated with a tumor is classified according to</td>
</tr>
</tbody>
</table>
the size of the tumor.

| T1: Tumor 2.0 cm or less in greatest dimension |
| T1mic: Microinvasion 0.1 cm or less in greatest dimension |
| T1a: Tumor more than 0.1 but not more than 0.5 cm in greatest dimension |
| T1b: Tumor more than 0.5 cm but not more than 1.0 cm in greatest dimension |
| T1c: Tumor more than 1.0 cm but not more than 2.0 cm in greatest dimension |

| T2: Tumor more than 2.0 cm but not more than 5.0 cm in greatest dimension |
| T3: Tumor more than 5.0 cm in greatest dimension |

| T4: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below. Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle. |
| T4a: Extension to chest wall |
| T4b: Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast |
| T4c: Both of the above (T4a and T4b) |
| T4d: Inflammatory carcinoma* |

**Regional lymph nodes (N):**

| NX: Regional lymph nodes cannot be assessed (e.g., previously removed) |
| N0: No regional lymph node metastasis |
| N1: Metastasis to movable ipsilateral axillary lymph node(s) |
| N2: Metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures |
| N3: Metastasis to ipsilateral internal mammary lymph node(s) |

**Pathologic classification (pN):**

| pNX: Regional lymph nodes cannot be assessed (not removed for pathologic study or previously removed) |
| pN0: No regional lymph node metastasis |
| pN1: Metastasis to movable ipsilateral axillary lymph node(s) |
| pNmi: Micrometastasis (larger than 0.2mm but no larger than 2.0mm) |
| pN1a: Only micrometastasis (none larger than 0.2 cm) |
| pN1b: Metastasis to lymph node(s), any larger than 0.2 cm |
| pN1bi: Metastasis in 1 to 3 lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension |
| pN1bii: Metastasis to 4 or more lymph nodes, any more than 0.2 cm and all less than 2.0 cm in greatest dimension |
| pN1biii: Extension of tumor beyond the capsule of a lymph node metastasis less than 2.0 cm in greatest dimension |
| pN1biv: Metastasis to a lymph node 2.0 cm or more in greatest dimension pN2: Metastasis to
<table>
<thead>
<tr>
<th>pN3:</th>
<th>Metastasis to ipsilateral internal mammary lymph node(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Distant metastasis (M):</strong></td>
</tr>
<tr>
<td>MX:</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0:</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1:</td>
<td>Distant metastasis present (includes metastasis to ipsilateral supraclavicular lymph nodes)</td>
</tr>
</tbody>
</table>