MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Genetic Assay of Tumor Tissue to Determine Prognosis of Breast Cancer (Oncotype Dx Breast Recurrence Score, MammaPrint)**
Policy Number	**2.02.27**
Category	**Technology Assessment**
Original Effective Date	**04/21/05**
Committee Approval Date	**04/20/06, 08/16/07, 10/23/08, 10/29/09, 12/16/10, 11/17/11, 11/15/12, 2/20/14, 01/22/15, 02/18/16, 03/16/17, 01/18/18, 03/21/19, 03/19/20, 5/21/20, 3/18/21, 1/20/22, 01/19/23**
Current Effective Date	**01/19/23**
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Archived Date	**NA**
Archive Review Date	**NA**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program(DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, including the National Comprehensive Cancer Network (NCCN) Guidelines, the use of the following assays to guide the decision about the need for adjuvant chemotherapy in patients with newly diagnosed breast cancer has been medically proven to be effective and, therefore, are considered **medically appropriate**:
   A. Oncotype Dx Breast Recurrence Score® or
   B. Mammaprint 70-gene panel;
   when ALL of the following criteria are met:
      1. Breast cancer is unilateral and non-fixed (not adherent to the chest wall).
      2. Breast cancer is hormone receptor positive (estrogen receptor (ER)-positive or progesterone receptor (PR)-positive).
      3. Breast cancer is human epidermal growth factor receptor 2 (HER2) negative.
      4. Tumor size is greater than 0.5 and up to one cm with moderate/poor differentiation or unfavorable features OR tumor size is greater than one cm (*refer to Policy Guidelines IV and V*).
      5. Tumor is Stage 1 or Stage 2.
      6. Breast cancer with involvement of three or fewer positive axillary nodes.
      7. There is no evidence of distant metastasis.
      8. The test result will determine the decision whether to treat the patient with adjuvant chemotherapy AND the affirmative decision to treat the breast cancer with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors) has been made.
      9. Chemotherapy is not precluded due to other factors.
      10. The assay is ordered within six months after diagnosis.

II. Based upon our criteria and assessment of the peer reviewed literature, the use of the following assays to guide the decision about the need for adjuvant chemotherapy in patients with newly diagnosed breast cancer has been medically proven to be effective and, therefore, are considered **medically appropriate**:
   A. Breast Cancer Index;
   B. Prosigna; or
   C. EndoPredict

   when ALL of the following criteria are met:
   1. Breast cancer is unilateral and non-fixed (not adherent to the chest wall).
   2. Breast cancer is hormone receptor positive (ER positive or PR positive).
   3. Breast cancer is HER2 negative.
   4. Tumor size is greater than 0.5 and up to one cm with moderate/poor differentiation or unfavorable features OR tumor size is greater than 1 cm (*refer to Policy Guidelines IV and V*).
   5. Tumor is Stage 1 or Stage 2.
   6. Breast cancer is axillary lymph node-negative.
   7. There is no evidence of distant metastasis.
   8. The test result will determine the decision whether to treat the patient with adjuvant chemotherapy AND the affirmative decision to treat with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors) has been made.
   9. Chemotherapy is not precluded due to other factors.
   10. The assay is ordered within six months after diagnosis.

III. Based upon our criteria and assessment of the peer-reviewed literature, including the NCCN Guidelines, the use of the Breast Cancer Index assay is considered **medically appropriate** to guide the decision about the need for extended endocrine therapy in patients diagnosed with breast cancer-when ALL of the following criteria are met:
   1. Breast cancer is hormone receptor positive (ER positive or PR positive) and HER2 negative.
   2. Breast cancer is axillary lymph node-negative.
   3. There is no evidence of distant metastasis.
   4. There is no evidence of cancer at the time of testing.
   5. The patient has been on endocrine therapy four or more years.
   6. The test results will determine the decision whether the patient is a candidate for extended endocrine therapy.

IV. Based upon our criteria and assessment of the peer reviewed literature, including the NCCN Guidelines, all other ~~uses~~ gene expression classifiers/risk scores have not been proven to improve health outcomes and, therefore, are considered **investigational** for patients diagnosed with breast cancer.

V. Based upon our criteria and review of the peer reviewed literature, including the NCCN Guidelines, all other gene expression profiling assays to select patients with early-stage breast cancer for adjuvant chemotherapy have not been medically proven to improve health outcomes and, therefore, are considered **investigational**.

VI. Based upon our criteria and assessment of the peer reviewed literature, the use of gene expression assays to molecularly subclassify breast cancer (e.g., BluePrint) are considered **investigational**.

VII. Based upon our criteria and assessment of the peer reviewed literature, the use of gene expression assays for quantitative assessment of ER, PR, and HER2 overexpression (e.g., TargetPrint) are considered **investigational**.

Refer to Corporate Medical Policy #2.02.30 Genotyping – Cytochrome P450 for Drug Metabolism.

Refer to Corporate Medical Policy #11.01.03 Experimental and Investigational Services.

Refer to Corporate Medical Policy #11.01.10 Clinical Trials.

POLICY GUIDELINES

I. Assays of genetic expression in tumor tissue are specialized tests that will likely be performed at a limited number of reference laboratories.

II. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

III. Gene expression classifiers/risk scores should only be ordered after surgery and subsequent pathology 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.

IV. Testing is limited to one test per lifetime.

V. Unfavorable features that may prompt testing in tumors from 0.6 to one cm in size include angiolymphatic invasion, high histologic grade, or high nuclear grade.

VI. Per the National Cancer Institute, risk categories for women with node-negative breast cancer are defined as:
   A. Low Risk: Tumor size is less than one cm, and tumor is estrogen receptor (ER) or progesterone receptor (PR) status-positive, and Tumor Grade is grade 1.
   B. Intermediate Risk: Tumor size is one to two cm, tumor is ER or PR status-positive, and Tumor Grade is grade 1 to 2.
   C. High risk: Tumor size is greater than two cm, or tumor is ER or PR status negative, or Tumor Grade is grade 2 to 3.

DESCRIPTION

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 for 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.

There has been interest in examining gene expression in tumor tissue as a prognostic factor. For example, ribonucleic acid (RNA) can be isolated from tumor tissue and used to generate complementary RNA, which is then labeled and allowed to hybridize to microarrays that can contain up to 25,000 human genes. Positive results are detected by fluorescent intensities. Patterns of genetic expression can then be compared to outcome databases to identify specific patterns associated with prognosis. Gene expression panels, or signatures, are an example of this technology.

Several gene expression breast cancer tests are commercially available in the U.S., including Oncotype Dx Breast Recurrence Score and MammaPrint. Other gene panels include Mammostrat (Clarient Diagnostic Services) and the Breast Cancer Index Test.

The Oncotype Dx Breast Recurrence Score (21-gene panel) (Genomic Health, Inc) uses a Recurrence Score (RS) calculated by a prespecified algorithm. It proposes to assess the likelihood of distant recurrence in women with stage I or II, node-negative, ER-positive breast cancer treated with tamoxifen. Gene expression profiles from a select panel of 21 genes in the patient's tumor tissue are analyzed using reverse transcription-polymerase chain reaction (RT-PCR). An algorithm is used to calculate an RS to categorize patients as low-risk (RS 18 or less), intermediate-risk (RS 18 to 31) or high-risk (RS 31 to 100).

The Breast Cancer Index test (bioTheranostics, Inc) is based on the ratio of the expression of two genes: the homeobox gene-B13 (HOXB13) and the interleukin-17B receptor gene (IL17BR). In breast cancers that are more likely to recur, the HOXB13 gene tends to be over-expressed, while the IL-17BR gene tends to be under-expressed.

The MammaPrint 70-gene panel (Agendia), which is sometimes referred to as the "Amsterdam signature," uses a customized, manufactured microarray. The gene signature identifies risk classification as high- or low-risk. MammaPrint was the first genetic test to assess breast cancer recurrence risk to be approved by the United States Food and Drug Administration (FDA). The test was approved on February 6, 2007.

BluePrint is an 80-gene expression assay that classifies breast cancer into types: basal, luminal, or HER2. The test is marketed as an additional stratifier into a molecular subtype after risk assessment with MammaPrint.

TargetPrint is a microarray-based gene expression test that offers a quantitative assessment of ER, PR, and HER2 overexpression in breast cancer. The test is marketed to be used in conjunction with MammaPrint and BluePrint.

EndoPredict (Myriad Genetic Laboratories, Inc) analyzes RNA expression of eight target genes, three normalization genes, and one control gene, creating a 12-gene molecular score, which is then combined with clinical features of the tumor (tumor size and nodal status) to predict the 10-year distant recurrence (DR) rate. This information assists treating physicians to guide therapy decisions by identifying which patients have sufficiently low risk of DR and may forgo chemotherapy, and which patients are at high risk for DR and may need adjuvant chemotherapy, in addition to endocrine therapy.

The Prosigna Breast Cancer Prognostic Gene Signature Assay (Veracyte, Inc) is an in vitro diagnostic assay that is performed on the NanoString nCounter Dx Analysis System using formalin-fixed paraffin-embedded (FFPE) breast tumor tissue previously diagnosed as invasive breast carcinoma. This qualitative assay utilizes gene expression data, weighted together with clinical variables to generate a risk category and numerical score. This is used to assess a patient's risk of distant recurrence of disease. The Prosigna Breast Cancer Prognostic Gene Signature Assay is indicated for use in female breast cancer patients who have undergone surgery in conjunction with locoregional treatment consistent with standard of care.

RATIONALE

The American Society of Clinical Oncologists (ASCO) paper on the Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer (2017) recommends the Oncotype Dx Breast Recurrence Score and Prosigna, to guide decisions on adjuvant systemic chemotherapy in a patients with ER/PR-positive, HER2-negative (node-negative) breast cancer (strength of recommendation: strong; evidence quality: high) as well as the EndoPredict, Mammaprint, and Breast Cancer Index (strength of recommendation: moderate; evidence quality: intermediate).

Oncotype Dx Breast Recurrence Score

In 2006, Paik, *et al.*, tested samples from a randomized controlled trial of ER-positive, node-negative breast cancer patients treated with tamoxifen versus tamoxifen plus chemotherapy by Oncotype Dx Breast Recurrence Score. This study provides supportive evidence for the use of this assay. Recurrence score (RS) high-risk patients derived clear benefit from chemotherapy, whereas the average benefit for other patients was statistically not significant, although the confidence intervals were wide and included the possibility of a small benefit.

Sparano et al. (2018) conducted the Trial Assigning Individualized Options for Treatment (TAILORx) to evaluate risk of recurrence in women with mid-range scores. Women with intermediate-risk scores were randomized to endocrine therapy (n=3399) or chemoendocrine therapy (n=3312). Women with low-risk scores 10 or lower) received endocrine therapy (n=1619) and women with high-risk scores (26 or greater) received chemoendocrine therapy (n=1389). Overall disease-free survival estimates showed that adjuvant endocrine therapy was noninferior to chemoendocrine therapy in women with intermediate-risk scores. However, subgroup analyses by age showed that women younger than age 50 years may benefit from chemotherapy.

The TAILORx, which was conducted in women with hormone receptor-positive, node-negative tumors and the Microarray in Node-Negative and one to three Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial, both phase II trials, provided the evidence for the American Society of Clinical Oncology (ASCO) 2019 update on

the Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Cancer.

The updated recommendations (Henry et al., 2019) for the Oncotype DX are for patients who present with hormone receptor–positive, HER-2 negative, axillary node–negative early breast cancer and include the following:

- For patients who are older than age 50 years and have tumors with Oncotype DX recurrence scores less than 26, and for patients who are age 50 years or younger and have tumors with Oncotype DX recurrence scores less than 16, there is little-to-no benefit from chemotherapy. Clinicians may offer endocrine therapy alone (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- For patients age 50 years or younger with Oncotype DX scores of 16 to 25, clinicians may offer chemoendocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
- Patients with Oncotype DX recurrence scores greater than 30 should be considered candidates for chemoendocrine therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with OncotypeDX scores of 26 to 30 (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

<u>MammaPrint Assay (Agendia, Inc)</u>

The 2017 ASCO Biomarkers Guideline (Henry et al., 2019) recommended the following:

- For patients who have ER or PR-positive, HER2-negative, node-negative breast cancer, and who are at high clinical risk per MINDACT categorization, the MammaPrint assay may be used to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- For patients who have ER or PR-positive, HER2-negative, node-negative breast cancer, and who are at low clinical risk per MINDACT categorization, the MammaPrint assay should not be used to inform decisions on withholding adjuvant systemic chemotherapy, because women in the low clinical risk category had excellent outcomes and did not appear to benefit from chemotherapy even with a genomic high-risk cancer (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- For patients who have ER or PR-positive, HER2-negative, node-positive breast cancer, with one to three positive nodes, and who are at high clinical risk per MINDACT categorization, the MammaPrint assay may be used to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good prognosis population with potentially limited chemotherapy benefit. However, such patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate).
- For patients who have ER or PR-positive, HER2-negative, node-positive breast cancer, the MammaPrint assay should not be used in patients with one to three positive nodes and at low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy. There are insufficient data on the clinical utility of MammaPrint in this specific patient population (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- For patients who have HER2-positive breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic therapy. Additional studies are required to address the role of MammaPrint in patients with this tumor subtype who are also receiving HER2-targeted therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- For patients who have ER or PR-negative and HER2-negative (triple-negative) breast cancer, the clinician should not use the MammaPrint assay to guide decisions on adjuvant systemic chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong).

<u>BluePrint and TargetPrint</u>

BluePrint is an 80-gene expression assay that discriminates among three breast cancer molecular subtypes; TargetPrint is a method to measure ER, PR, and HER2 as an alternative to immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). The clinical utility of BluePrint is unknown, as it is unclear how this test will add to treatment decision making using currently available, accepted methods (e.g., clinical and pathologic parameters). The incremental benefit of using TargetPrint as an alternative to current standard methods of measuring ER, PR, and HER2 has not been demonstrated, nor is it included in recommendations for testing issued by the American Society of Clinical Oncology (ASCO) or the College of American Pathologists.

Mammostrat is an IHC test intended to evaluate risk of breast cancer recurrence in post-menopausal, node-negative, ER-positive breast cancer patients who will receive hormonal therapy and are considering adjuvant chemotherapy. The test employs five monoclonal antibodies to detect gene expression of proteins involved in various aspects of cell proliferation and differentiation and a proprietary diagnostic algorithm to classify patients into high-, moderate-, or low-risk categories. One study reports the development of the assay but provides no information on technical performance (analytic validity). In an independent cohort, a multivariable model predicted 50%, 70%, and 87% five-year disease-free survival for patients classified as high, moderate, and low prognostic risk, respectively, by the test results (p=0.0008). There are no published reclassification studies of comparison with conventional risk classifiers.

The 2022 National Comprehensive Cancer Network (NCCN) guidelines for Breast Cancer indicate that the 21-gene Oncotype Dx Breast Recurrence Score, Mammaprint 70-gene panel, Breast Cancer Index, Prosigna, and EndoPredict are gene expression assays for consideration of adjuvant systemic therapy that may provide prognostic and therapy-predictive information that complements stage (T), lymph node (N), metastases (M), and biomarker information. Oncotype Dx is preferred by the NCCN Breast Cancer Panel for node-negative breast cancer. The recurrence score from any of these assays should be used for decision making only in the context of other elements of risk stratification for an individual patient (Recommendations: I for Oncotype Dx and Mammaprint; 2A for EndoPredict, Prosigna, and Breast Cancer Index). For Oncotype Dx, a secondary analysis of a prospective trial suggests that the test is predictive for women with one to three involved ipsilateral axillary lymph nodes (RxPONDER). The Breast Cancer Index assay is predictive of benefit of extended adjuvant endocrine therapy. Other gene expression assays have not proven to be predictive of chemotherapy benefit. There are few data regarding the role of gene expression assays in women with four or more ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors. Use of molecular assays in men with breast cancer have limited data to assess prognosis and to predict benefit from chemotherapy. Available data suggest the 21-gene Oncotype Dx assay recurrence score provides prognostic information in men with breast cancer.

The 2021 NCCN recommendations for consideration of adjuvant systemic therapy include the following:
Oncotype Dx
Patients with T1b/c and T2, HR-positive, HER2-negative, pN0 tumors, with risk scores (RS) between 0-10 have a risk of distant recurrence of less than 4%. Those with RS of 11 to 25, derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study. In those patients 50 or less years of age with RS of 16 to 25, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distance recurrence compared with endocrine monotherapy. Consideration should be given for the addition of chemotherapy to endocrine therapy in this group.

For patients with T1b/c and T2, HR-positive, HER2-negative, pN+tumors, the RS is prognostic in those patients receiving endocrine monotherapy. A secondary analysis of a prospective registry of patients with HR-positive, HER2-negative, pN+ tumors with an RS of less than 18 demonstrated a five-year risk of distant recurrence of 2.7% when treated with endocrine monotherapy. In the West German Plan B study, 110 women with HR-positive, HER2-negative, pN+ tumors and RS of less than 11 showed a five-year disease-free survival of 94.4% when treated with endocrine therapy. For HR-positive, HER2-negative, pN+ tumors, clinicians should be aware that the optimal RS cut-off (less than 11 versus less than 18) is still unknown for prognosis (risk of recurrence) as well as prediction of chemotherapy benefit. In a secondary analysis of the SWOG 8814 trial of patients with HR-positive, pN+ tumors, an RS of 31 or greater was predictive of chemotherapy benefit. Because of a higher risk of distant recurrence, patients who are HR-positive and have one to three positive lymph nodes and an RS of 19 or greater, should be considered for adjuvant chemotherapy in addition to endocrine therapy.

MammaPrint
With a median follow-up of five years, among patients either lymph node negative or node positive, at high clinical risk and low genomic risk, the rate of survival without distant metastasis in this group was 94.7% (95% CI, 92.5%-96.2%) among those who did not receive adjuvant chemotherapy. Among patients with one to three positive lymph nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1%-98.1%) in those who received adjuvant chemotherapy versus 95.6% (95% CI, 92.7-97.4) in those who did not receive adjuvant chemotherapy. Therefore, the additional benefit of adjuvant chemotherapy may be small in this group.

Prosigna
For patient with T1 and T2 HR-positive, HER2-negative, pN0 tumors, a risk of recurrence score in the low range, regardless of tumor size, places the tumor into the same prognostic category as T1a to T1b, N0, M0. In patients with HR-positive, HER2-negative, pN+ tumor, (one to three positive lymph nodes) with low risk of recurrence score, treated with endocrine therapy alone, the distant recurrence risk was less than 3.5% at 10 years and no distant recurrence was seen at 10 years in the TransATAC study in a similar group (Sestak et al., 2018).

EndoPredict
For patient with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a 12-gene low-risk score, regardless of tumor size, places the tumor into the same prognostic category as T1a to T1b, N0, M0. In the Austrian Breast Cancer Study Group (ABCSG), six of eight patients in the low-risk group had risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with one to three positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years (Sestak et al., 2019). The assay is prognostic in endocrine and chemo-endocrine treated patients.

Breast Cancer Index (BCI)
For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a BCI in the low-risk range of 0 to five, regardless of tumor size, places the tumor into the same prognostic category as T1a to T1b, N0, M0. Patients with BCI low result demonstrated a lower risk of distant recurrence (compared to BCI high) and no significant improvement in disease-free-survival (DFS) or overall survival (OS) compared to the control arm in terms of extending endocrine therapy duration. For patients with T1 HR-positive, HER2-negative, and pN0 tumors, a BCI of 5.1 to 10 demonstrated significant rates of late distant recurrence. In secondary analyses of the MA 17, Tran-aTTom, and IDEAL trials, patients with HR-positive, T1 to T3, pN0 or pN+, who were BCI high, demonstrated significant improvements in disease-free survival (DFS) when adjuvant endocrine therapy was extended, compared to the control arm. In contrast, BCI low patients derived no benefit from extended adjuvant therapy (Noordhoek et al., 2020).

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy (Breast Cancer Index, Biotheranostics, Inc)

Code	Description
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score (Oncotype Dx Breast Recurrence Score, Genomic Health, Inc)
81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score (Prosigna, Veracyte)
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis (Mammaprint, Agendia)
81522	Oncology (breast), MRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score (EndoPredict, Myriad Genetics, Inc)
81523	Oncology, mRNA, next-generation sequencing gene expression profiling (Mammaprint NGS, Agendia, Inc)
0153U	Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement (Insight TNBCtype, Insight Molecular Labs)
0220U **(E/I)**	Oncology (breast cancer), image analysis with artificial intelligence assessment of 12 histologic and immunohistochemical features, reported as a recurrence score (PreciseDx Breast Cancer Test; PreciseDx)
0404U **(E/I)**	Oncology (breast), semiquantitative measurement of thymidine kinase activity by immunoassay, serum, results reported as risk of disease progression *(effective 10/01/2023)*
0418U **(E/I)**	Oncology (breast), augmentative algorithmic analysis of digitized whole slide imaging of 8 histologic and immunohistochemical features, reported as a recurrence score *(effective 10/01/2023*)

HCPCS Codes

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

ICD10 Codes

Code	Description
C50.011-C50.019	Malignant neoplasm of nipple and areola, female (code range)
C50.111-C50.119	Malignant neoplasm of central portion of breast, female (code range)
C50.211-C50.219	Malignant neoplasm of upper-inner quadrant of breast, female (code range)

Code	Description
C50.311-C50.319	Malignant neoplasm of lower-inner quadrant of breast, female (code range)
C50.411-C50.419	Malignant neoplasm of upper-outer quadrant of breast, female (code range)
C50.511-C50.519	Malignant neoplasm of lower-outer quadrant of breast, female (code range)
C50.611-C50.619	Malignant neoplasm of axillary tail of breast, female (code range)
C50.811-C50.819	Malignant neoplasm of overlapping sites of breast, female (code range)
C50.911-C50.919	Malignant neoplasm of breast of unspecified site, female (code range)
C79.81	Secondary malignant neoplasm of breast
C79.89-C79.9	Secondary malignant neoplasm of other specified and unspecified sites (code range)
D05.00-D05.92	Carcinoma in situ of breast (code range)
D48.60-D48.62	Neoplasm of uncertain behavior of breast (code range)
D49.3	Neoplasm of unspecified behavior of breast

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*Key Article

KEY WORDS

Breast cancer gene expression ratio, Blueprint®, MammaPrint, Mammostrat, Oncotype DX, Targetprint, 70-gene profile, Rotterdam signature, 21-gene panel, 70-gene panel, Prosigna

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=133&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AAQAAAIAIAAA&

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