MEDICAL POLICY

Medical Policy Title	**Genetic Assay of Tumor Tissue to Determine Prognosis and Treatment of Breast Cancer**
Policy Number	**2.02.27**
Current Effective Date	April 17, 2025
Next Review Date	April 2026

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

Newly Diagnosed Breast Cancer

I. The use of the following assays to guide the decision about the need for adjuvant chemotherapy are considered **medically appropriate**:

   A. Oncotype Dx Breast Recurrence Score; **or**

   B. Mammaprint 70-gene panel;

   when **ALL** the following criteria are met:

   1. Breast cancer is unilateral;
   2. Breast cancer is hormone receptor positive (estrogen receptor (ER)-positive and/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 cm and up to 1 cm with moderate/poor differentiation or unfavorable features OR tumor size is greater than 1 cm;
   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 decision to treat the breast cancer with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors) has been discussed as a treatment option;
   9. Chemotherapy is not precluded due to other factors; **and**
   10. The assay is ordered within six (6) months after diagnosis.

II. The use of the following assays to guide the decision about the need for adjuvant chemotherapy are considered **medically appropriate**:

   A. Breast Cancer Index;

B. Prosigna; **or**

C. EndoPredict

when **ALL** the following criteria are met:

1. Breast cancer is unilateral;
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 cm and up to 1 cm with moderate/poor differentiation or unfavorable features **OR** tumor size is greater than 1 cm;
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 decision to treat with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors) has been discussed as a treatment option;
9. Chemotherapy is not precluded due to other factors; **and**
10. The assay is ordered within six months after diagnosis.

Extended Endocrine Therapy

III. 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** the following criteria are met:

A. Breast cancer is hormone receptor positive (ER positive or PR positive) and HER2 negative;

B. Breast cancer is axillary lymph node-negative or node-positive with one to three (1-3) positive nodes;

C. There is no evidence of distant metastasis;

D. There is currently no evidence of cancer;

E. The patient has been on endocrine therapy four or more years; **and**

F. The test results will determine the decision whether the patient is a candidate for extended endocrine therapy.

Gene Expression

IV. All other gene expression classifiers/risk scores (e.g., Oncotype DX Breast DCIS Score Test, DCISionRT and PreciseDx) are considered **investigational** for patients diagnosed with breast cancer.

V. All other gene expression profiling assays to select patients with early-stage breast cancer for adjuvant chemotherapy are considered **investigational**.

VI. The use of gene expression assays to molecularly subclassify breast cancer (e.g., BluePrint) are considered **investigational**.

VII. The use of gene expression assays for quantitative assessment of ER, PR, TKa and HER2 overexpression (e.g., TargetPrint, DiviTum TKa blood test) are considered **investigational**.

RELATED POLICIES

Corporate Medical Policy

2.02.30 Pharmacogenetics

11.01.03 Experimental or Investigational Services

11.01.10 Clinical Trials

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

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

V. Testing is limited to one (1) test per lifetime.

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

VII. 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 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 Oncotype DX Breast DCIS Score uses information from 12 of the 21 genes assayed in the standard Oncotype DX test for early breast cancer to predict ten-year risk of local recurrence (DCIS or invasive carcinoma).

DCISionRT uses breast tissue from a biopsy or surgery to estimate the risk of recurrence of ductal carcinoma in situ (DCIS) or invasive carcinoma in a patient with DCIS as well as the benefit of adjuvant radiation therapy. The DCISionRT test combines seven monoclonal protein markers (COX-2,

FOXA1, HER2, Ki-67, p16/INK4A, PR, and SIAH2) assessed in tumor tissue with four clinicopathologic factors (age at diagnosis, tumor size, palpability, and surgical margin status) to produce a score that stratifies patients with DCIS into three risk groups: low risk, elevated risk with good response, and elevated risk with poor response.

The PreciseDx Breast Cancer Test is designed to provide image analysis with artificial intelligence assessment of 12 histologic and immunohistochemical features, reported as a recurrence score.

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.

DiviTum TKa is a blood-based biomarker test that monitors and predicts treatment response in hormone receptor-positive metastatic breast cancer. The DiviTum TKa blood test measures thymidine kinase activity (TKa) which reflects cell proliferation.

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.

SUPPORTIVE LITERATURE

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.

Sparano et al. (2022), the TAILORx investigators, provided an update in 2023 which confirmed findings from this primary analysis. With a median follow-up of at least 10.4 years for the overall population and 11 years for the randomized population, the study confirmed the prognostic capability of the Oncotype DX assay using all pre-specified survival endpoints. Differentiation between RS categories in all the endpoints was highly significant ($p<0.001$). In the intermediate RS 11–25 arms, 12-year DFS analysis identified no advantage of chemoendocrine therapy (77.4 ± 0.9%) versus ET alone (76.8 ± 0.9%), confirming non-inferiority for the primary endpoint. Non-inferiority for chemoendocrine therapy was maintained for distant recurrence, and OS.

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 aged 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).

Oncotype DX Breast DCIS Score Test

In 2013, Solin et al. conducted a prospective-retrospective analysis of the Oncotype DX breast cancer assay that was performed for patients with DCIS treated with surgical excision without radiation in the Eastern Cooperative Oncology Group (ECOG) E5194 study. The primary objective was to determine whether the continuous DCIS Score was statistically significantly associated with the risk of an IBE (defined as local recurrence of DCIS or invasive carcinoma in the ipsilateral breast). The continuous DCIS Score was statistically significantly associated with the risk of developing an IBE (hazard ratio [HR] = 2.31, 95% confidence interval [CI] = 1.15 to 4.49; P = .02) when adjusted for tamoxifen use and with invasive IBE (unadjusted HR = 3.68, 95% CI = 1.34 to 9.62; P = .01). For the prespecified DCIS risk groups of low, intermediate, and high, the 10-year risks of developing an IBE were 10.6%, 26.7%, and 25.9%, respectively, and for an invasive IBE, 3.7%, 12.3%, and 19.2%, respectively (both log rank P ≤ .006). The results of this Simon et al. (2009) category B level of evidence study suggest that DCIS score may help select patients who should undergo adjuvant radiation. However, further validation is required before becoming a part of clinical practice.

DCISionRT

In 2021, Warnberg et al. conducted a prospective-retrospective analysis of the SweDCIS randomized controlled trial which enrolled 504 women who were diagnosed with DCIS from 1987-2000. 504 women had complete data and negative margins, 52% (n=264/504) of participants were categorized as elevated risk, 48% (n=240/504) as low risk. In the low-risk group, there was no significant difference in risk of recurrence observed with radiotherapy. Radiotherapy was associated with reduced risk of total and invasive ipsilateral recurrence in the elevated risk group. In the Elevated Risk group, RT significantly decreased relative 10-year ipsilateral total recurrence (TotBE) and 10-year ipsilateral invasive recurrence (InvBE) rates, HR 0.32 and HR 0.24, with absolute decreases of 15.5% and 9.3%. In the low-Risk group, there were no significant risk differences observed with radiotherapy. Using a cutoff of DS > 3.0, the test was not predictive for RT benefit (p = 0.093). This Simon et al (2009) category B study provided clinical validity which showed no benefit of radiation therapy among those classified as low risk. However, estimated ten-year recurrence risk of this group is unclear whether this is low enough to consider altering clinical management. Further clinical validation and utility is warranted.

Precise DX

There is currently a lack of evidence and literature to support that the use of PreciseDX would improve health outcomes.

Divitum TKa

Bergqvist et al. (2023) state that serum thymidine kinase activity (TKa) levels, an indicator of cell-proliferation, is a potential biomarker for monitoring endocrine therapy (ET) and predicting metastatic breast cancer (MBC) outcome. The authors examined data on progression within 30/60 days post sampling, with a new, FDA approved version of DiviTum TKa highlighting differences versus a Research Use Only version. The evaluation included 1,546 serum samples from 454 patients, collected at baseline and at 4 subsequent timepoints during treatment. A predefined cut-off tested the ability to predict disease progression. A new measuring unit, DuA (DiviTum® unit of Activity) was adopted. The authors found that a DiviTum TKa score less than 250 DuA provides a much lower risk of progression within 30/60 days after blood draw, the negative predictive value (NPV) was 96.7% and 93.5%, respectively. Patients less than 250 DuA experienced significantly longer progression-free survival and overall survival, demonstrated at baseline and for all time intervals. The authors concluded that DiviTum TKa provides clinically meaningful information for patients with HR+ MBC, and that low TKa levels provide such a high NPV for rapid progression that such patients might forego additional therapy added to single agent ET. Further research is warranted.

There is currently a lack of evidence and literature to support that the use of Divitum TKa would improve health outcomes.

MammaPrint Assay (Agendia, Inc)

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).

BluePrint and TargetPrint

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.

Wuerstlein et al. (2019) conducted a prospective evaluation of how MammaPrint and BluePrint influence clinical therapy decisions in patients with luminal early breast cancer. About 72% (309 out of 430) of patients had node-negative disease. Specifically focusing on BluePrint's impact, the investigators found that there was a 65% concordance rate between IHC assessment and BluePrint subtyping for Luminal A or B-like tumors. Notably, BluePrint reclassified two clinically identified Luminal A-like tumors and four Luminal B-like tumors as Basal type. Additionally, BluePrint reclassified 46% (80 out of 173) of Luminal B-like tumors to Luminal A, and 24% (62 out of 256) of Luminal A-like tumors to Luminal B. This led to an overall discordance rate of 34% in subtype classification.

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, Nitz et al. (2019) 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

The Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial (Cardoso et al., 2016) is a prospectively designed trial evaluating MammaPrint, with additional randomized components. Currently, 5-year results are available. In this trial, women with early-stage breast cancer were evaluated with both MammaPrint and a clinical risk estimator. Women at low risk with both methods did not receive chemotherapy. Women with discordant risks were randomized to chemotherapy or to no chemotherapy. Women at high-risk with both methods received chemotherapy.

The group at high clinical risk and low genomic risk who did not receive chemotherapy had a distant recurrence rate of 5.3% (95% CI, 3.8% to 7.5%). In the node-negative, estrogen receptor-positive, or HER2-negative subgroup analysis, this group had a distant recurrence rate of 4.5% (95% CI, 3.8% to 8.4%). Piccart et al., 2021 reported updated results from MINDACT. In the updated analysis, with median follow-up of 8.7 years (IQR 7.8 to 9.7), 5-year distant metastasis-free survival rate for patients with high clinical risk and low genomic risk receiving no chemotherapy (primary test population, n=644) was 95.1% (95% CI 93.1% to 96.6%), supporting the previous analysis.

In the group with clinical low-risk and high genomic risk, who were not considered in the main outcome, in both the main analysis and in the node-negative, estrogen receptor-positive, or HER2-negative subgroup, the results would indicate that the risk of distant recurrence is not low enough to avoid chemotherapy (main analysis distant recurrence, 5% [95% CI, 3% to 8.2%]; hazard ratio (HR) subgroup distant recurrence, 6.1% [95% CI, 3.9% to 9.4%]). In the testing strategy implied in this study, by not testing for genomic risk in the low clinical risk group, these patients would not be identified.

The groups randomized to chemotherapy showed no significant difference in 5-year distant recurrence, but the CIs were wide and thus less informative regarding whether chemotherapy is or is

not beneficial in these patient groups. In the main study, the HR for chemotherapy in the high clinical risk/low genomic risk was 0.78 (95% CI, 0.5 to 1.21). The HR for chemotherapy in the low clinical risk/high genomic risk group was 1.17 (95% CI, 0.59 to 2.28).

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 (1) to three (3) 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 (5), 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).

Male Breast Cancer

For males with breast cancer, the evidence for Oncotype DX (21-gene signature) includes only one systematic review and meta-analysis of retrospective cohort studies (Davey et al, 2022), focused on Oncotype DX in both female and male patients with ER-positive, HER2-negative early breast cancer. No studies were identified evaluating the EndoPredict, Breast Cancer Index, MammaPrint/BluePrint, or Prosigna tests in male breast cancer patients.

Davey et al. (2022) conducted a systematic review and meta-analysis of retrospective cohort studies, focusing on 21-gene assay scores (Oncotype Dx) in both female and male patients with ER-positive, HER2-negative early breast cancer. The analysis included six studies with a total of 176,338 patients.

Only 1% of the patients had male breast cancer (MBC). Male patients were observed to have higher tumor stages, increased nodal involvement, and a greater incidence of grade 3 disease (all $p < 0.001$). Overall, the likelihood of male patients having 21-gene assay scores <18 (OR: 1.04, 95% CI: 0.94–1.16) and scores between 18-30 (OR: 1.12, 95% CI: 1.00–1.26) was comparable to that of female patients. The findings of this meta-analysis should be interpreted with caution due to the small number of male patients included in the studies. MBC patients analyzed had a higher tumor burden and grade compared to female patients. Furthermore, without stage matching between male and female breast cancer, drawing meaningful conclusions regarding 21-gene assay scores is challenging. The retrospective nature of the studies contributes to inherent limitations such as ascertainment, confounding, and selection biases. Future research on Oncotype Dx should include its validation in an MBC population to establish its clinical usefulness.

PROFESSIONAL GUIDELINE(S)

The American Society of Clinical Oncology (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).

In 2022, ASCO published updated clinical practice guidelines on the use of breast cancer biomarker assay results to guide adjuvant endocrine and chemotherapy decisions in early-stage breast cancer. The updated recommendations include:

- Clinicians may use Oncotype DX, MammaPrint, Breast Cancer Index, and EndoPredict to guide adjuvant endocrine and chemotherapy in patients who are post-menopausal or aged >50 with early-stage ER+ and HER2- breast cancer that is node-negative or with one to three (1-3) positive nodes.
- Prosigna and Breast Cancer Index may be used in postmenopausal patients with node-negative ER+ and HER- breast cancer.
- In premenopausal patients, clinicals may use Oncotype in patients with node-negative ER+ and HER2- breast cancer.
- There are no data on use of genomic tests to guide adjuvant chemotherapy in patients with > four (4) positive nodes.

The V1.2025 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. Trans-aTTom, and IDEAL trials showed that in patients with HR-positive T1–T3 tumors that are lymph-node negative or positive, those that had a high BCI (H/I) demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared to the control arm. 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. The terms males and females are used to denote sex assigned at birth. Due to the limited participation of males in breast cancer clinical trials, the recommendations for managing breast cancer in males are predominantly based on extrapolations from data obtained from female breast cancer trials. Although there are some biological and clinical differences between breast cancer in males and females, the management of breast cancer in males generally mirrors that of females, with specific considerations for male patients. 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.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Oncotype DX and other tests listed herein are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In 2007, MammaPrint (Agendia) was cleared for marketing by the FDA through the 510(k) process for the prediction of breast cancer metastasis. In 2015, MammaPrint was cleared for marketing by the FDA through the 510(k) process for use in fresh-frozen, paraffin-embedded breast cancer tissue.

In 2013, Prosigna was cleared for marketing by the FDA through the 510(k) process. Moreover, the FDA determined that Prosigna was substantially equivalent to MammaPrint.

Currently, the Breast Cancer Index (Biotheranostics), EndoPredict (distributed by Myriad) and DCISionRT (PreludeDX) are not FDA cleared or approved.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than

policy updates).

- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

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.)
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 of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis (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)
0295U (E/I)	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2),

Code	Description
	with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a recurrence risk score (DCISionRT, PreludeDx, Prelude Corporation)
0404U (E/I)	Oncology (breast), semiquantitative measurement of thymidine kinase activity by immunoassay, serum, results reported as risk of disease progression (DiviTum TKa blood test, Biovica Inc)
0418U (E/I)	Oncology (breast), augmentative algorithmic analysis of digitized whole slide imaging of 8 histologic and immunohistochemical features, reported as a recurrence score (PreciseDx Breast Cancer Test; PreciseDx)
0045U (E/I)	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score (The Oncotype DX Breast DCIS Score Test, Genomic Health, Inc)

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)
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)

Code	Description
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

SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

LCD - Molecular Pathology Procedures (L35000) [accessed 2025 Jan 23]

Article - Billing and Coding: Molecular Pathology Procedures (A56199) [accessed 2025 Jan 23]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.

- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, 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 HISTORY/REVISION	
Committee Approval Dates	
04/20/06, 08/16/07, 10/23/08, 10/29/09, 12/16/10, 11/17/11, 11/15/12, 02/20/14, 01/22/15, 02/18/16, 03/16/17, 01/18/18, 03/21/19, 03/19/20, 05/21/20, 03/18/21, 01/20/22, 01/19/23, 03/21/24, 03/20/25, 04/17/25	
Date	**Summary of Changes**
04/17/25	• Off-cycle review. Policy criteria edited: 'Breast cancer is unilateral' and 'the test result will determine the decision whether to treat the patient with adjuvant chemotherapy AND the decision to treat the breast cancer with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors) has been discussed as a treatment option'
03/20/25	• Annual update. Section titles added within policy statement section. PS. III edited to include "Node-positive with one to three (1-3) positive nodes. PS.III.D edited to read "There is currently no evidence of cancer."
01/01/25	• Summary of changes tracking implemented.
04/21/05	• Original effective date