Gene Expression Testing for Breast Cancer Prognosis

Policy Number: AHS – M2020 – Gene Expression Testing for Breast Cancer Prognosis
Initial Presentation Date: 1/1/2020
Revision Date: 5/1/2020

Temporary Modification of Coverage Criteria due to COVID-19:

In response to the recent coronavirus (COVID-19) outbreak, Blue Cross Blue Shield of Kansas City has temporarily approved an expansion to the coverage criteria of this policy related to the requirements that gene expression assays must be conducted on a surgical specimen and nodal status provided. Many elective and non-essential surgical procedures have been delayed due to the COVID-19 outbreak. This coverage criteria modification supports the continued diagnosis and treatment of members despite restrictions due to COVID-19.

In particular, Blue Cross Blue Shield of Kansas City has temporarily approved the use of genetic expression test on core biopsies without nodal status until December 31, 2020 or earlier if elective and/or non-essential surgeries resume.

Policy Description

Gene expression assays measure the amount of specific mRNAs being transcribed to assess the genes that are active in a particular cell or tissue. Analyses of gene expression can be clinically useful for disease classification, diagnosis, prognosis, and tailoring treatment to underlying genetic determinants of pharmacologic response (Steiling, 2019).

Adjuvant systemic therapy has reduced mortality from breast cancer (Davies et al., 2011; Peto et al., 2012). Several breast tumor gene expression assays have been developed to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer (Harris et al., 2016; Theodoros & Bergh, 2020).

Related Policies

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Policy Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHS-M2003</td>
<td>BRCA</td>
</tr>
<tr>
<td>AHS-G2054</td>
<td>Detection of Circulating Tumor Cells and Cell Free DNA in Cancer Management</td>
</tr>
<tr>
<td>APEA-G2059</td>
<td>Epithelial Cell Cytology In Breast Cancer Risk Assessment</td>
</tr>
<tr>
<td>AHS-G2124</td>
<td>Serum Tumor Markers For Malignancies</td>
</tr>
<tr>
<td>AHS-M2126</td>
<td>Use Of Common Genetic Variants (Single Nucleotide Polymorphisms) To Predict Risk Of Non-Familial Breast Cancer</td>
</tr>
</tbody>
</table>
Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

1. Use of the Oncotype DX 21-gene expression, EndoPredict, or PAM50 (Prosigna) assay is considered MEDICALLY NECESSARY for the determination of the recurrence of risk for deciding whether or not to undergo adjuvant chemotherapy in individuals with primary, invasive breast cancer who meet all of the following criteria:
   a. Node-negative (lymph nodes with micrometastases [less than two mm in size] are considered node negative for this policy statement) OR with 1-3 involved ipsilateral axillary lymph nodes when test results would impact treatment decisions
   b. Hormone receptor positive (either estrogen-receptor [ER] or progesterone-receptor [PR] positive)
   c. Human epidermal growth factor receptor two (HER2) negative
   d. Tumor size > 0.5 cm
   e. Histology is ductal, lobular, mixed or metaplastic
   f. Staging pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2mm axillary node metastasis)
      • The assay should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy).
      • For patients who otherwise meet the above characteristics but who have multiple primary tumors, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

2. Use of Mammaprint to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy is considered MEDICALLY NECESSARY in women with high clinical risk per MINDACT categorization with primary, invasive breast cancer with the same characteristics as considered medically necessary for Oncotype DX (1a – 1f).

3. Tumor testing for hormone receptor (Estrogen Receptor and Progesterone Receptor) expression and Human Epidermal Growth Factor Receptor 2 (HER2) overexpression is considered MEDICALLY NECESSARY for all women with newly diagnosed, non-metastatic breast cancer.

4. Use of Mammaprint to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy IS CONSIDERED NOT MEDICALLY NECESSARY in women with low clinical risk per MINDACT categorization with primary, invasive breast cancer.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.

5. In males, use of gene expression assays other than 21-gene RT-PCR-based assays is CONSIDERED EXPERIMENTAL AND INVESTIGATIONAL.
6. Use of other gene expression assays including, but not limited to Mammostrat, **IS CONSIDERED EXPERIMENTAL AND INVESTIGATIONAL**.

7. The use of Oncotype DX for DCIS **IS CONSIDERED EXPERIMENTAL AND INVESTIGATIONAL**.

8. Use of all other tests than 21-gene Oncotype Dx for pN0 or Node-negative for predictive purposes **IS CONSIDERED EXPERIMENTAL AND INVESTIGATIONAL**.

**Scientific Background**

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women. In the United States, breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer death in women. Approximately 1 in 8 women will develop breast cancer in their lifetime (Siegel, Miller, & Jemal, 2019; Taghian & Merajver, 2020).

Adjuvant systemic therapy has reduced mortality from breast cancer (Darby et al., 2011; Davies et al., 2011; Forouzanfar et al., 2011; Peto et al., 2012). However, adjuvant therapy is not without its risks and costs. Reliable prognostic profiles for recurrence and clinically applicable predictive factors would be of great value in the use of adjuvant therapy by identifying which therapies would be most likely of benefit to patients and which patients would not benefit (Theodoros & Bergh, 2020).

Several biology-based prognostic profiles have been developed, validated, and are in clinical use to predict breast cancer response to chemotherapy. Intensive research efforts are ongoing to refine the clinical utility and the indications for these prognostic profiles (Simon, Paik, & Hayes, 2009). In addition, as next generation sequencing of tumor genomes progresses, these profiles will be improved or replaced by the next generation of molecular profiles (Theodoros & Bergh, 2020).

Chen et al examined the association of genomic methylation and the changes in the subsequent transcriptome. The authors desired to observe how a chronic condition influenced epigenomic changes. A human volunteer provided peripheral blood samples over 36 months, and the authors created 28 methylome datasets as well as 57 transcriptome datasets. During this period, the human volunteer experienced 6 viral infections and two elevated periods of fasting glucose and glycated hemoglobin A1c. The authors noted that the methylome changes correlated with the glucose level changes, and that the gene expression levels varied greatly, often during the viral infections. The authors proposed that the DNA methylation was the primary gene expression mechanism for chronic conditions, as it was generally a stable epigenetic marker (Chen et al., 2018).

Rueda et al presented a disease model that stratifies distinct stages and incorporated factors such as "locoregional recurrence, distant recurrence, breast-cancer-related death and death from other causes". This model integrated these features into an individual risk-of-recurrence prediction. This model was applied to 3240 patients, of which 1980 had molecular data. From this model, the authors identified four late-recurring "integrative subtypes, comprising about one quarter (26%) of tumours that are both positive for ER and negative for human epidermal growth factor receptor 2, each with characteristic tumour-driving alterations in genomic copy number and a high risk of recurrence (mean 47–62%) up to 20 years after diagnosis". These four subtypes were "enriched" in copy number alterations, and these alterations were labeled the "likely drivers" of each subgroup. A triple negative subgroup "IntCluster 10" was found to be largely relapse-free after 5 years whereas the "IntCluster4 ER negative" subgroup was found to have a large risk of recurrence (Rueda et al., 2019).

**OncoType DX**
The Oncotype Dx 21-gene recurrence score (RS) is the best-validated prognostic assay and may identify patients who are most and least likely to derive benefit from adjuvant chemotherapy. The expression levels of 16 genes (plus five reference genes) are measured by quantitative reverse transcription polymerase chain reaction (RT-PCR). The sum of this calculation is known as the RS to optimize prediction of distant relapse despite tamoxifen therapy. At this time, it is indicated for women with node-negative, estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer to determine the prognosis in patients recommended to proceed with at least a five-year course of endocrine therapy. The optimal RS cutoff for omission of chemotherapy remains unclear given that the different studies have used different cutoffs (Mamounas et al., 2010; Paik et al., 2004; Paik et al., 2006; Sparano et al., 2015). However, it may be reasonable not to administer adjuvant chemotherapy for patients with node-negative, ER-positive breast cancer and an RS of <15 (Theodoros & Bergh, 2019, 2020).

Sparano et al (2018) performed a prospective trial to assess the utility of the recurrence score based on the 21 gene breast cancer assay to predict chemotherapy in patients who have a midrange score. "Of the 9719 eligible patients with follow-up information, 6711 (69%) had a midrange recurrence score of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. The trial was designed to show noninferiority of endocrine therapy alone for invasive disease-free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death)." They found that "Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease-free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.08; 95% confidence interval, 0.94 to 1.24; P=0.26). At 9 years, the two treatment groups had similar rates of invasive disease-free survival (83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group), freedom from disease recurrence at a distant site (94.5% and 95.0%) or at a distant or local-regional site (92.2% and 92.9%), and overall survival (93.9% and 93.8%). The chemotherapy benefit for invasive disease-free survival varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25." They concluded that "Adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger (Sparano et al., 2018)."

EndoPredict

EndoPredict® (Myriad Genetic, Inc.) is a breast cancer prognostic test that assesses the expression of eight target genes as compared to three housekeeping (normalization) genes and one additional control gene to detect contamination by residual DNA. The results of this testing are combined to produce a clinical score to determine whether the breast cancer is at high- or low-risk of possible recurrence within ten years (Myriad, 2020; Warf et al., 2017).

According to the Myriad EndoPredict® Technical Specifications (Effective Date: 12/10/2019), if the test is used on resected tissue, the 12-gene molecular score is then "combined with tumor size and lymph node status to generate an EPclin Risk Score associated recurrence risks and estimated absolute benefit of chemotherapy" whereas "the molecular score and its associated 10-year risk of distance recurrence...are provided" if the sample is a biopsy specimen (Myriad, 2019). The target genes in the EndoPredict® test include the following (Filipits et al., 2019; Warf et al., 2017):

- **BIRC5**
- **DHCR7**
- **UBE2C**
Filipits et al validated EP’s 11 gene version (only missing the one gene to control for DNA contamination, HBB). The investigators combined these gene expression results with nodal status and tumor size into a risk score (“EPClin”). Two cohorts of 378 and 1324 samples were used in this study, and both cohorts demonstrated that the risk score produced was an independent predictor of distant recurrence. The investigators calculated that EPClin had superior prognostic power compared to solely clinicopathologic factors. EPClin was also found to result in a 4% rate of recurrence for both low-risk cohorts in each sample, a 28% recurrence rate in the “high risk” portion of the 378-item sample, and a 22% recurrence rate in the “high risk” portion of the 1324-item sample. The authors concluded that “the multigene EP risk score provided additional prognostic information to the risk of distant recurrence of breast cancer patients, independent from clinicopathologic parameters. The EPclin score outperformed all conventional clinicopathologic risk factors (Filipits et al., 2011; Myriad, 2017).”

Two recent studies by Sestak and colleagues have also shown the clinical validity and utility of EndoPredict® testing in women with node-positive breast cancer (Sestak et al., 2018; Sestak et al., 2019). One study consisted of both node-positive and node-negative women (n=3746) to compare the performance of EPclin for predicting distant recurrence in women who had either received endocrine therapy (ET) alone or ET with chemotherapy (ET+C). “In this comparative non-randomised analysis, the rate of increase in DR with EPclin score was significantly reduced in women who received ET+C versus ET alone. Our indirect comparisons suggest that a high EPclin score can predict chemotherapy benefit in women with ER-positive, HER2-negative disease (Sestak et al., 2019).” In the other study, the researchers compared the performance of six different prognostic signatures for ER-positive breast cancer in two different patient groups—node-negative and node-positive. The six tests include EndoPredict®, Breast Cancer Index (BCI), Clinical Treatment Score (CTS), IHC4, ROR, and RS. Within the node-positive cohort (n=277), the authors report the highest univariate hazard ratio (HR) for EPclin (1.69) compared to 1.39 for RS (Sestak et al., 2018).

Another study (n=1702) compared the use of EndoPredict® in node-positive and node-negative women treated with endocrine therapy only. This study assessed both the 10- and 15-year distant recurrence-free rate (DRFR). Similar to the node-negative individuals, the 10-year DRFR for patients with 1 – 3 positive nodes improved significantly higher than for the full cohort (95.6% versus 80.9%, respectively). “The molecular and EPclin scores were significant predictors of DRFR after adjusting for clinical variables, regardless of nodal status (Filipits et al., 2019).”

**Breast Cancer Index**

The Breast Cancer Index (BCI) is a combination of two profiles, the HOXB13-to-IL17BR expression ratio (H:I ratio) and the Molecular Grade Index (MGI). This combination is intended to report “the individualized likelihood of benefit from extended endocrine therapy” and “the individualized risk of late distant recurrence of breast cancer (Years 5 - 10)” . The five genes the MGI examines are BUB1B, CENPA, NEK2, RACGAP1, and RRM2 (Biotheranostics, 2018). Using genome-wide microarray analysis, three differentially expressed genes that were associated with an increased risk of progression among ER-positive patients treated with tamoxifen were: the antiapoptotic homeobox B13 (HOXB13, overexpressed in tamoxifen recurrent cases) and
both interleukin 17B receptor (IL17BR) and EST AI240933 (both overexpressed in tamoxifen nonrecurrent cases) (Theodoros & Bergh, 2019).

This test was validated by Ma et al. The MGI was validated by separate 410-sample and 323-sample cohorts, and its interaction with the H:I ratio was evaluated. The authors found that “high MGI was associated with significantly worse outcome only in combination with high HOXB13:IL17BR, and likewise, high HOXB13:IL17BR was significantly associated with poor outcome only in combination with high MGI.” The investigators concluded that “the combination of MGI and HOXB13:IL17BR outperforms either alone and identifies a subgroup (∼30%) of early stage estrogen receptor–positive breast cancer patients with very poor outcome despite endocrine therapy (Ma et al., 2008)."

**Predictor Analysis of Microarray 50**

The Predictor Analysis of Microarray 50 (PAM50, by Prosigna) is a 50-gene test that characterizes an individual tumor by intrinsic subtype. It was designed to determine the intrinsic subtype of a cancer using only 50 prespecified genes. The four subtypes are “luminal A, luminal B, HER2-enriched, and basal-like” (Parker et al., 2009). Results from the PAM50 are used to generate the risk of recurrence (ROR) score, which can stratify patients with ER-positive disease into high, medium, and low subsets. The test can be performed on formalin-fixed, paraffin-embedded tissue with a high degree of analytical validity (Nielsen et al., 2010; Theodoros & Bergh, 2019).

This test was validated by Parker et al. The investigators developed this 50-gene set from 189 prototype samples and evaluated 761 patients for prognosis. The four discrete subtypes were found to be prognostically significant and predicted neoadjuvant chemotherapy efficacy with a negative predictive value for pathologic complete response (to a taxane and anthracycline regimen) of 97%. The authors concluded “diagnosis by intrinsic subtype adds significant prognostic and predictive information to standard parameters for patients with breast cancer (Parker et al., 2009).”

**MammaPrint**

MammaPrint is a 70-gene test that assesses the risk of recurrence within the first 5-10 years of diagnosis. The test reports risk in one of two categories, “low” and “high”. MammaPrint’s validation places “low” risk at a 1.3% chance (95% confidence interval: 0-3.1%) that cancer will recur in 5 years whereas those classified as “high” risk have a 11.7% chance for the cancer to recur in 5 years (95% confidence interval: 6.6%-16.8%) (Agendia, 2015, 2018). Agendia offers other breast cancer assessments, such as BluePrint. BluePrint is an 80-gene molecular subtyping assay, which “analyzes the activity” of its genes. It is proposed to identify a tumor’s molecular “subtype”: luminal A/B, basal, or HER2. Each subtype has varying molecular characteristics (ER-positive or negative, HER2-positive or negative, et al), which is proposed to help clinicians provide targeted treatment for a patient (Agendia, 2019).

MammaPrint was validated by Cardoso et al. The authors determined the risk recurrence of 6693 patients. Of these 6693 patients, 1550 of them were found to have high clinical risk and low genomic risk, and the rate of survival without distant metastasis in this cohort was 94.7% among those not receiving chemotherapy. The difference in survival rate between these patients and those receiving chemotherapy was 1.5%. The authors estimated that “given these findings, approximately 46% of women with breast cancer who are at high clinical risk might not require chemotherapy” (Fatima Cardoso et al., 2016).

**Clinical Utility**

Blok et al performed a meta-analysis of the MammaPrint, OncotypeDX, PAM50/Prosigna and Endopredict assays. The authors investigated the evidence available on both the clinical utility and economic value of these assays. Most of the observed studies concluded that genomic
profiling contributed to less chemotherapy use. However, the authors caution that “absolute numbers should be interpreted carefully, since some tests are less frequently studied than others” especially as “the clinical consensus on adjuvant chemotherapy is that we are most likely over-treating our patients, since we are not capable of identifying patients that will or will not benefit from chemotherapy using the current clinicopathological parameters”. The authors note that Petkov et al. retrospectively matched OncoType DX use with SEER registry data for over 40000 patients and found that “patients with node negative, HR+, HER2- breast cancer which underwent testing (n = 40,134, 22.7% chemotherapy) had no lower chemotherapy use compared to patients that were not tested (n = 144,056, 22.2% chemotherapy)”. The authors noted that 90% of the 44 economic analyses concluded that genomic testing was cost-effective; although, various biases are mentioned (publication bias, publications using overlapping samples, and more) (Blok et al., 2018).

Gustavsen performed an economic analysis of the Breast Cancer Index. “Costs associated with adjuvant chemotherapy, toxicity, followup, endocrine therapy, and recurrence were modeled over 10 years. The models examined cost utility compared with standard practice when used at diagnosis and in patients disease-free at 5 years post diagnosis.” The authors calculated BCI to save approximately $3803 per patient for the newly diagnosed population and $1803 per patient in the 5 years post diagnosis population. These savings were projected to come from “adjuvant chemotherapy use, extended endocrine therapy use, and endocrine therapy compliance” (Gustavsen et al., 2014).

Camp et al investigated a new reinterpretative technique of the PAM50 assay. The authors reorganized the gene expression data provided by the assay into five “quantitative, orthogonal, multi-gene breast tumor traits” and stated that these “dimensions” better represented breast cancer pedigrees. They re-assessed the data of the GEICAM/9906 clinical trial with these dimensions. After reorganization, the authors concluded that dimensions “PC1 and PC5” were associated with disease-free survival, and low “PC3 and PC4” indicated response to paclitaxel. However, high PC3 or PC4 did not show survival advantage (Camp et al., 2019).

Wuerstlein et al evaluated the clinical utility of MammaPrint and its intended adjunct test, BluePrint. Physicians were asked to provide initial therapy recommendations (based on clinicopathological factors), then were provided results of MammaPrint/BluePrint risk stratifiers. Then the same physicians provided new treatment recommendations, and the subsequent treatment was recorded. The authors identified a switch in treatment in 29.1% of cases. Physician adherence to MammaPrint risk assessment was over 90% in both groups of risk (low and high). Even when physicians and risk stratifiers disagreed, the physicians tended to recommend treatments based on the risk stratifier. Overall, the authors concluded that “MammaPrint and BluePrint test results strongly impacted physicians’ therapy decisions in luminal EBC with up to three involved lymph nodes” (Wuerstlein et al., 2019).

Toole et al evaluated the similarities and differences in genetic profiles between primary breast cancers in patients with multiple primaries. The authors also evaluated whether obtaining genetic profiling scores (OncoType DX) on each primary affected chemotherapy decisions. 22 patients had multiple tumor samples sent for analysis, and the authors found that 6 patients had their chemotherapy recommendations changed based on differing OncoType scores (between their samples). The authors also noted that scores tended to differ more between tumors appearing simultaneously on different breasts compared to multiple tumors on the same breast (Toole, Kidwell, & Van Poznak, 2014).

Another study published in 2016 compared the use of EndoPredict® (EPclin) and PAM50 risk of recurrence (ROR) scores in node-positive breast cancer to predict distant metastasis-free survival (MFS). ROR scores can be based using subtype (ROR-S); subtype and proliferation (ROR-P); subtype and tumor size (ROR-T); and subtype, proliferation, and tumor size combined (ROR-PT). “Predictors including clinical information showed superior prognostic performance compared to molecular scores alone (10-year MFS, low-risk group: ROR-T 88 %; ROR-PT 92
A recent study by Ding et al (Ding et al., 2019) specifically used the 21-gene recurrence score for patients with pure mucinous breast cancer (PMBC). This multi-year study of 8048 female PMBC patients categorized the patients based on RS risk groups of low, intermediate, and high RS risk groups. They found the distribution to be 64.9%, 31.9%, and 3.2%, respectively. For PMBC patients, the authors note that PMBC patients do show significantly different 5-year survival rates based on ER status. They do conclude that RS can be used with PMBC patients...

• age, progesterone receptor status, and grade could independently predict RS” (Ding et al., 2019). These data support the findings of a considerably smaller comparative study (n=35 PMBC patients and n=70 IDC patients) that show on average PMBC patients score lower than IDC patients (average RS 21.26 and 24.40, respectively); however, they authors do conclude that “patients with high RS in the PMBC group might be recommended to receive adjuvant chemotherapy” since 8.57% of PMBC patients have RS scores within the highest risk stratification (W. Wang et al., 2018). Both studies contradict an earlier, smaller study (n=10 TC patients and n=33 MC patients) that reported no patients within the high-risk RS category (Turashvili et al., 2017).

A large retrospective study of various subtypes of T1-T2N0 estrogen receptor-positive breast cancer (n=83665) was published in 2018. Both mucinous and tubular histologies were included in the study. The authors note considerable differences in RS scores between the various histologies; for example, they found that 1.0% and 28.5% of tubular adenocarcinoma patients had RS scores in the high and intermediate ranges, respectively, whereas mucinous adenocarcinoma patients fared worse with 3.4% and 28.8%, respectively. It should be noted, however, that only 2.1% of the patients included in the study had been diagnosed with mucinous adenocarcinoma and 0.6% with tubular adenocarcinoma (J. Wang et al., 2018). Similarly, a study by Kizy et al also reported that 4% of tubular carcinoma patients were classified as high risk based on the Trial Assigning Individualized Options for Treatment RS criteria (Kizy et al., 2018).

An in-depth systemic review of the effectiveness and cost-effectiveness of Oncotype DX®, MammaPrint®, Prosigna®, EndoPredict®, and immunohistochemistry 4 (IHC4) was released in 2019 (Harnan et al., 2019). For this review, the authors included a total of 153 studies, including the MINDACT RCT for MammaPrint. The authors note that a limitation of this systemic review, and of the current field in general, is that only one RCT has been completed to date. Their results include the following:

• “There is limited and varying evidence that oncotype DX and MammaPrint can predict benefit from chemotherapy.”

• “The health economic analysis suggests that the incremental cost-effectiveness ratios for the tests versus current practice are broadly favourable for the following scenarios: (1) oncotype DX, for the LN0 subgroup with a Nottingham Prognostic Index (NPI) of > 3.4 and the one to three positive lymph nodes (LN1–3) subgroup (if a predictive benefit is assumed); (2) IHC4 plus clinical factors (IHC4+C), for all patient subgroups; (3) Prosigna, for the LN0 subgroup with a NPI of > 3.4 and the LN1–3 subgroup; (4) EndoPredict Clinical, for the LN1–3 subgroup only [emphasis added]; and (5) MammaPrint, for no subgroups (Harnan et al., 2019).”

Guidelines and Recommendations

American Society of Clinical Oncology (ASCO)

In 2016, ASCO provided recommendations on appropriate use of breast tumor biomarker assay results to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer. ASCO recommends that “in addition to estrogen and progesterone receptors and human epidermal growth factor receptor 2, the panel found sufficient evidence of clinical utility
for the biomarker assays Onco type DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1 in specific subgroups of breast cancer (Harris et al., 2016).”

ASCO also made the following recommendations:

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the 21-gene recurrence score to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 21-gene RS to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.

- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the 21-gene RS (EndoPredict), to guide decisions on adjuvant systemic therapy.

- If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the Breast Cancer Index, the PAM50-ROR, the 12-gene risk score, or the 21-gene RS (EndoPredict), to guide decisions on adjuvant systemic therapy.

- If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use urokinase plasminogen activator (uPA), plasminogen activator inhibitor type 1 (PAI-1), the Breast Cancer Index, the PAM50 risk of recurrence (ROR) score, the 12-gene risk score (EndoPredict), and the 21-gene recurrence score (Oncotype DX) to guide decisions on adjuvant systemic therapy. If the patient has had 5 years of endocrine therapy without evidence of recurrence, the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, or IHC4) to guide decisions on extended endocrine therapy.

- If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use uPA, IHC4, the 12-gene risk score (EndoPredict), PAI-1, the 21-gene RS (Oncotype DX), the five-protein assay (Mammostrat), the Breast Cancer Index or TILs to guide decisions on adjuvant systemic therapy. The clinician should not use circulating tumor cells (CTCs) to guide decisions on adjuvant systemic therapy

- If a patient has HER2-positive breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy.

- If a patient has TN breast cancer, the clinician should not use the PAM50-ROR to guide decisions on adjuvant systemic therapy (Harris et al., 2016).

In 2017 the ASCO (Krop et al., 2017), based on a review of the MINDACT study publication, revised their guidelines on Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer to state:

“Recommendation 1.1.1 (update of Recommendation 1.7).
If a patient has ER/PgR-positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay may be used in those with high clinical risk per MINDACT categorization 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; Evidence quality: high; Strength of recommendation: strong).
**Recommendation 1.1.2 (update of Recommendation 1.7).**
If a patient has ER/PgR–positive, HER2-negative, node-negative, breast cancer, the MammaPrint assay should not be used in those with low clinical risk per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy as 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; Evidence quality: high; Strength of recommendation: strong).

**Recommendation 1.2.2: (update of 2016 recommendation 1.7)**: If a patient has ER/PgR–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).

**Recommendation 1.3: (update of 2016 recommendation 1.8):** If a patient has 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).

**Recommendation 1.4: (update of 2016 recommendation 1.9):** If a patient has ER/PgR 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) (Krop et al., 2017)

ASCO published an update in 2019 regarding decisions to be made regarding therapy based on OncoType score. However, they did not change the recommendations made in 2016 or 2017 (Andre et al., 2019).

ASCO published an update regarding the “Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer”, which was released in response to the results of two phase III trials, MINDACT and TAILORx. The updated guidelines state that the clinical trials found evidence of clinical utility for both node-positive and node-negative patients, but only for patients determined to be at high clinical risk. Therefore, the Panel did not recommend use of MammaPrint for patients determined to be of low clinical risk (Henry et al., 2019).

**American Joint Committee on Cancer**
The Expert Panel determined that:

“Multigene panels may provide prognostic and therapy predictive information that complements T, N, M and biomarker information. Use of these assays is not required for staging. The Breast Expert Panel included one multigene panel in Pathological Prognostic Staging, but others may be equally useful for clinical decision making. Inclusion in the staging system does not imply recommendation or endorsement of one multigene panel over any other for use in clinical care (ACS, 2018).”

**Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group**
In 2009, the EGAPP found “insufficient evidence to make a recommendation for or against the use of tumor gene expression profiles to improve outcomes in defined populations of women with breast cancer (EGAPP, 2009).”
With regard to MammaPrint, EGAPP found “that data were adequate to support an association between the MammaPrint Index and 5- or 10-year metastasis rates, but the relative efficacy of testing in ER-positive and -negative women is not clear. Study subjects were European, and how characteristics of other demographic populations might affect test performance is not known (EGAPP, 2009).”

Also, with regard to the H:I test, EGAPP found that “the evidence available to assess clinical validity is inadequate, with a small number of studies in a variety of heterogeneous populations, and only one study that applies directly to the laboratory-developed test offered by Quest (EGAPP, 2009).”

The 2016 EGAPP Working Group guidelines state that there is “insufficient evidence to recommend for or against the use of Oncotype DX testing to guide chemotherapy treatment decisions in women with hormone receptor–positive, lymph node–negative, or lymph node–positive early breast cancer who are receiving endocrine therapy.” The guidelines further state that “with regard to clinical utility, although there was evidence from prospective retrospective studies that the Oncotype DX test predicts benefit from chemotherapy, and there was adequate evidence that the use of Oncotype DX gene expression profiling in clinical practice changes treatment decisions regarding chemotherapy, no direct evidence was found that the use of Oncotype DX testing leads to improved clinical outcomes (EGAPP, 2015).”

**National Comprehensive Cancer Network (NCCN)**

The 2020 v3 NCCN guidelines on Breast Cancer, when referring to EndoPredict®, give a 2A recommendation for its use with node-negative and 1 – 3 nodes as a prognostic assay, but they list only Oncotype Dx as a predictive assay. Concerning EndoPredict®, they go on to state, “In ABCSG 6/8, patients in the low-risk group had risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1 – 3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 1 years. The risk score is predictive of chemo-benefit based on a prospective analysis of 3,746 archived, HR-positive, HER2-negative, T1 – T3 tumors from chemo-endocrine and endocrine-only cohorts, that included women with lymph node-negative and lymph node-positive disease (NCCN, 2020a).”

The NCCN guidelines on Breast Cancer (NCCN, 2020b) state that “the 21-gene RT-PCR assay recurrence score can be considered in select patients with 1-3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy”.

**The NCCN strongly recommends (Category 1)** to consider the use of the 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay for determining the use of adjuvant chemotherapy in patients with the following tumor characteristics:

- Hormone receptor-positive;
- HER2 [human epidermal growth factor receptor 2]-negative;
- Ductal, lobular, mixed or metaplastic histology;
- pT1, pT2 or pT3 stage; and pN0 or pN1mi (≤ 2mm axillary node metastasis);
- Tumor >0.5 cm.

In regard to other multigene assays, the NCCN guidelines state: “other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy” (NCCN, 2020b).

The NCCN states that MammaPrint, PAM50, EndoPredict, and Breast Cancer Index may all be considered (at an evidence and consensus level of “2A”) for prognosis of “adjuvant systemic chemotherapy to adjuvant endocrine therapy”. Both PAM50 and EndoPredict have this evidence and consensus level for both node-negative and 1-3 positive node cases. Furthermore,
OncoType has a 2A evidence and consensus level of 2A for use for prognostic use for pN+ or node positive cases (NCCN, 2020b).

"The NCCN Panel members acknowledge that many assays have been clinically validated for prediction of prognosis. However, based on the currently available data, the panel believes that the 21-gene assay has been best validated for its use as a prognostic test as well as in predicting who is most likely to respond to systemic chemotherapy" (NCCN, 2020b).

Within a section on special considerations for breast cancer in men, the NCCN states (Category 2A), "Data are limited regarding the use of molecular assays to assess prognosis and to predict benefit from chemotherapy in men with breast cancer. Available data suggests 21-gene assay recurrence score provides prognostic information in men with breast cancer (NCCN, 2020b)."

NCCN also notes that ER status should be determined for DCIS patients, but do not mention any gene expression tests for evaluation (NCCN, 2020b).

Regarding tubular or mucinous types of breast cancer, the NCCN notes that the ER and PR status of the tumor is crucial and likely to be positive. The NCCN recommends a re-test if a tubular, mucinous, or papillary subtype is found to be ER- and PR-, but if the tumor is truly ER- and PR-, the tumor should be treated as if it were of “usual” histology (ductal, lobular, mixed, metaplastic). If the tumor is ER+/PR+, then the same stages above apply (NCCN, 2020b).

A request from Genomic Health to review OncoType DCIS for potential inclusion in NCCN guidelines was denied in September 2018. The vote was 21 "No" and 7 "Abstain". A similar request was denied in August 2019, with 24 "No" and 5 "Absent" (NCCN, 2020c).

National Institute for Health and Care Excellence (NICE, 2018)

NICE released three new guidelines regarding gene expression tests, which are as follows:

1. “EndoPredict (EPclin score), Oncotype DX Breast Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative (including micrometastatic disease; see section 5.4) early breast cancer, only if:
   - they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index
   - information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy taking into account their preference
   - the companies provide the tests to the NHS with the discounts agreed in the access proposals and
   - clinicians and companies make timely, complete and linkable record-level test data available to the National Cancer Registration and Analysis Service as described in the data collection arrangements agreed with NICE (see section 5.29).”

2. MammaPrint is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because it is not cost effective (NICE, 2018).

European Society for Medical Oncology (ESMO)

ESMO notes that “In cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of other tests), gene expression assays, such as MammaPrint, Oncotype DX, Prosigna and EndoPredict, may be used, where available. These assays can determine the individual’s recurrence risk as well as potentially predict the benefit of chemotherapy”. This point was unchanged in the 2019 update (F. Cardoso et al., 2019; Senkus et al., 2015).”
In a 2019 update, ESMO elaborates on gene expression profiles for breast cancer. They state that "Gene expression profiles, such as MammaPrint, Oncotype DX Recurrence Score, Prosigna and Endopredict, may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict the benefit of adjuvant chemotherapy". They also remark that Prosigna, Endopredict, and Oncotype are intended for ER-positive early breast cancer only and that Mammmaprint and OncoType are still being evaluated for clinical utility (F. Cardoso et al., 2019).

**European Group on Tumor Markers (EGTM, 2017)**

EGTM notes several gene expression profiles as having clinical utility regarding adjuvant chemotherapy.

- uPA/PAI-1, Oncotype DX, MammaPrint, Prosigna, EndoPredict and BCI may be used for avoiding adjuvant chemotherapy in ER-positive, HER2-negative and lymph node–negative patients.
- Oncotype DX, MammaPrint, Prosigna and EndoPredict may also be used for avoiding adjuvant chemotherapy in ER-positive, HER2-negative and lymph node–positive patients (1–3 positive nodes) (Duffy et al., 2017).

**State and Federal Regulations, as applicable**

MammaPrint® was U.S. Food and Drug Association (FDA)-approved on June 22, 2007. MammaPrint® is performed in Agendia laboratories in the Netherlands and in California. MammaPrint is FDA cleared for use in women under 61, with stage 1 or 2 breast cancer, invasive carcinoma, tumor size ≤5 cm, and lymph node negative (FDA, 2007).

Prosigna™ received 510(k) clearance from FDA based on substantial equivalence to MammaPrint® on September 6, 2013 (FDA, 2013).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ‘88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

**Applicable CPT/HCPCS Procedure Codes**

<table>
<thead>
<tr>
<th>Code Number</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81518</td>
<td>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 <strong>Proprietary test:</strong> Breast Cancer Index <strong>Lab/manufacturer:</strong> Biotheranostics, Inc.</td>
</tr>
<tr>
<td>81519</td>
<td>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 <strong>Proprietary test:</strong> Oncotype DX® <strong>Lab/manufacturer:</strong> Genomic Health</td>
</tr>
<tr>
<td>81520</td>
<td>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 <strong>Proprietary test:</strong> Prosigna® Breast Cancer Assay</td>
</tr>
<tr>
<td>Procedure Code</td>
<td>Lab/manufacturer:</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------</td>
</tr>
</tbody>
</table>
| 81521         | NanoString Technolo| 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  
**Proprietary test:** MammaPrint® |
| 81522         | Agendia, Inc.      | 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  
**Proprietary test:** EndoPredict® |
| 81599         | Myriad Genetic Laboratories, Inc. | Unlisted multianalyte assay with algorithmic analysis  
**Proprietary test:** EndoPredict® |
| 84999         |                   | Unlisted chemistry procedure |
| 88360         |                   | Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual |
| 88361         |                   | Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology |
| 88367         |                   | Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure |
| 88368         |                   | Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), manual, per specimen; initial single probe stain procedure |
| 88381         |                   | Microdissection (ie, sample preparation of microscopically identified target); manual |
| S3854         |                   | Gene expression profiling panel for use in the management of breast cancer treatment |
| 0045U         | Genomic Health, Inc. | 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  
**Proprietary test:** Oncotype DX® Breast DCIS Score™ |
| 0053U         | Insight Molecular Labs | 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  
**Proprietary test:** Insight TNBCtype™ |

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

**Evidence-based Scientific References**


**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/20</td>
<td>New Policy</td>
<td>Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following modifications to the coverage criteria. Removed the word “ipsilateral” from the bulleted sub-point regarding staging (based on NCCN guidelines). Added language regarding the lack of published literature (for old E&amp;I CCs). In accordance to NCCN guidelines, added Coverage Criteria stating, “Use of all other tests than 21-gene Oncotype Dx for pN0 or Node-negative for predictive purposes IS CONSIDERED INVESTIGATIONAL.” Codes 81522 and 0153U were added.</td>
</tr>
<tr>
<td>5/1/20</td>
<td></td>
<td>New CC1: added &quot;EndoPredict, or PAM50 (Prosigna)&quot;. CC1: 21-gene RT PCR and Oncotype DX were removed because CC1 already says &quot;Use of the Oncotype DX 21-gene expression&quot;. Old CC2: based on 2020 NCCN guidelines, this CC is now combined with CC1 for clarity since all tests are recommended by NCCN for both node-positive and node-negative breast cancers.</td>
</tr>
</tbody>
</table>
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.