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Corporate Medical Policy

Gene Expression Testing for Breast Cancer Prognosis AHS - M2020

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TEMPORARY EXPANSION OF COVERAGE FOR GENE EXPRESSION PROFILING TESTING ALLOWING ONCOTYPE DX 21-GENE EXPRESSION ASSAY TO BE PERFORMED ON A BREAST CORE BIOPSY:

The following is in response to recommendations for "Prioritization, Treatment and Triage of Breast Cancer Patients During the COVID-19 Pandemic" made by **The COVID-19 Pandemic Breast Cancer Consortium** (composed of **r**epresentatives from the American Society of Breast Surgeons (ASBrS), the National Accreditation Program for Breast Centers (NAPBC), the National Comprehensive Care Network (NCCN), the Commission on Cancer (CoC), and American College of Radiology (ACR)), who issued the following treatment recommendation for a subset of newly-diagnosed, early stage, invasive breast cancer patients:

Patients with ER+, HER2- tumors can defer surgery and receive neoadjuvant endocrine therapy for 6 to 12 months without clinical compromise. Patients should be assessed periodically to confirm absence of tumor progression. Patients with Stage 1 or limited Stage 2 disease (including those with N1 nodal involvement), and those with low-intermediate grade tumors, lobular breast cancer, low-risk genomic assays (especially the recurrence score, which may be sent from a core biopsy), or "luminal A" signatures, do not benefit substantially from neoadjuvant or adjuvant chemotherapy. These patients may receive endocrine therapy alone.

Policy

Blue Cross Blue Shield North Carolina (BCBSNC) may consider use of the Oncotype DX 21-gene expression assay performed on a breast core biopsy **medically necessary** in women with primary, invasive breast cancer when used to decide to defer surgery during the COVID pandemic, when all of the following criteria are met:

a) Tumor is hormone receptor positive (either estrogen-receptor [ER] or progesterone-receptor [PR] positive)

b) Tumor is human epidermal growth factor receptor 2 (HER2) negative

c) Tumor size > 0.5 cm

d) Histology is ductal, lobular, mixed or metaplastic

e) Disease is clinical stage 1 or limited stage 2 (to include cN1)

- *For patients who otherwise meet the above characteristics but who have multiple ipsilateral 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.*

These changes are effective during the COVID-19 pandemic effective from April 27, 2020 through June 30, 2021. We will reevaluate if an additional extension is needed as we approach June 30.

Description of Procedure or Service

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 (Spira, 2017).

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, 2017).

Related Policies:
BRCA AHS-M2003
Detection of Circulating Tumor Cells and Cell Free DNA in Cancer Management AHS-G2054
Epithelial Cell Cytology in Breast Cancer Risk Assessment AHS-G2059
Serum Tumor Markers for Malignancies AHS-G2124
Use of Common Genetic Variants to Predict Risk of Non-Familial Breast Cancer AHS-M2126

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for gene expression testing for breast cancer prognosis when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Gene Expression Testing for Breast Cancer Prognosis is covered

Gene expression testing for breast cancer prognosis is considered medically necessary for the following indications:

1. Use of the Oncotype DX 21-gene expression assay for the determination of the recurrence of risk for deciding whether or not to undergo adjuvant chemotherapy in women 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 2 (HER2) negative

D. Tumor size > 0.5 cm
E. Histology is ductal, lobular, mixed or metaplastic
F. Staging pT1, pT2, or pT3; and pN0, pN1mi (≤ 2 mm axillary node metastasis), or pT1.
   - *The 21-gene RT-PCR assay Oncotype DX 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 ipsilateral 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 EndoPredict or PAM50 (Prosigna), to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer with the same characteristics as considered for Oncotype DX (1a– 1f); (with one exception—for individuals with 1-3 involved ipsilateral axillary lymph nodes the tests are considered investigational).

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

Reimbursement for tumor testing for hormone receptor (Estrogen Receptor and Progesterone Receptor) expression and Human Epidermal Growth Factor Receptor 2 (HER2) overexpression is allowed for all women with newly diagnosed, non-metastatic breast cancer.

When Gene Expression Testing for Breast Cancer Prognosis is not covered

1. Use of Mammaprint to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with low clinical risk per MINDACT categorization with primary, invasive breast cancer is considered investigational.

2. Use of gene expression assays in men are considered investigational.

3. Use of other gene expression assays including, but not limited to, Mammostrat**,** is considered investigational

4. Use of Oncotype DX for DCIS is considered investigational.

Policy Guidelines

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(Taghian, El-Ghamry, & Merajver, 2017).

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 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, 2017).

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 (Banerji et al., 2012; CGAN, 2012; Curtis et al., 2012; Ding et al., 2010; Ellis et al., 2012; Shah et al., 2012; Theodoros & Bergh, 2017)

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 is reasonable not to administer adjuvant chemotherapy for patients with node-negative, ER-positive breast cancer and an RS of <18. (Theodoros & Bergh, 2017)

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."

EndoPredict (EP) utilizes reverse transcriptase polymerase chain reaction (PCR) of 11 genes (including three reference genes) to calculate a prognostic score. EP appears to be useful in the identification of a subgroup of patients with ER-positive, HER2-negative tumors that have a very low risk of recurrence without adjuvant chemotherapy(Dubsky et al., 2013) and appears to identify patients at low risk for a late recurrence (Dubsky et al., 2013; Theodoros & Bergh, 2017)

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). 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) (Coffin, 1995; Ma et al., 2004).

The Predictor Analysis of Microarray 50 (PAM50, by Prosigna) is a 50-gene test that characterizes an individual tumor by intrinsic subtype (Parker et al., 2009). It was designed to determine the intrinsic subtype of a cancer using only 50 prespecified genes. 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, 2017)

Urokinase plasminogen activator (uPA) is a serine protease with an important role in cancer invasion and metastases (Stephens, Brunner, Janicke, & Schmitt, 1998). When bound to its receptor (uPAR), uPA converts plasminogen into plasmin and mediates degradation of the extracellular matrix during tumor cell invasion.

High levels have been associated with shorter survival in women with breast cancer (Chappuis et al., 2001; Foekens et al., 2000; Malmstrom et al., 2001; Stephens et al., 1998). ASCO guidelines include the option for using uPA and PAI-1 to guide decisions on adjuvant systemic therapy for patients with node-negative, hormone-positive/HER2-negative disease, but not for patients with HER2-positive or triple-negative disease (Harris et al., 2016; Theodoros & Bergh, 2017).

See Table.

Test	Oncotype DX Genomic Health breast cancer prognostic test	MammaPrint Agendia breast cancer prognostic test	EndoPredict Myriad breast cancer prognostic test
Intended use	The test is intended for use in all newly diagnosed patients with early-stage (stage I, II or IIIa), breast cancer who have node-negative or node-positive (1-3), estrogen receptor-positive (ER+), HER2-negative disease to predict chemotherapy benefit	The test is indicated for breast cancer patients with: Breast Cancer Stage 1 or2; invasive carcinoma (infiltrating carcinoma); tumor size ≤5.0cm; lymph node negative; ER+ or ER-; HER2 neg or pos	The test is intended for use in patients with estrogen receptor-positive (ER+), human epidermal growth factor 2-negative (HER2-), early-stage breast cancer, node-negative or node-positive (1-3 positive nodes)
Score calculation	Gene expression results are used to generate a score that is a number between 0-100. A low score means the cancer has a lower chance of returning and patient has a lower chance of benefiting from chemotherapy. A high score means the cancer has a higher chance of returning and patient has a higher chance of benefiting from chemotherapy. For example, patients with a high score often choose more aggressive treatment options including chemotherapy, than patients with low scores.	Provides a numerical index with a range of -1 to +1, that is overlayed with a binary Low Risk / High Risk clinical classification system. The clinical classification threshold was set by the determination of the largest population of Low Risk patients that can safely withhold chemotherapy.	Combination of gene expression results score with the cancer's size and nodal status to calculate an EPclin Score that categorizes the cancer as having either a high risk or low risk of distant recurrence.
Number of genes tested	21-gene signature	70-gene signature	12-gene signature
Technology	RT-PCR	microarray	RT-PCR
FDA status	Not FDA approved	Approved in 2007	Not FDA approved
Societies recognizing clinical utility	ASCO, EGAP, NCCN, NICE, ESMO	ASCO	ASCO

State and Federal Regulations, as applicable

MammaPrint® was U.S. Food and Drug Association (FDA)-approved on February 6, 2007. MammaPrint® is performed in Agendia laboratories in the Netherlands and in California. MammaPrint is FDA cleared for use in women of all ages, with stage 1 or 2 breast cancer, invasive carcinoma, tumor size <5 cm, lymph node negative, estrogen receptor positive or negative, and HER2/neu positive or negative.

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

Other Breast Cancer Prognosis panels are considered laboratory developed tests (LDT); developed, validated and performed by individual laboratories.

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.

Guidelines and Recommendations

American Society of Clinical Oncology (ASCO)

In 2007, the ASCO stated that, "In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from tamoxifen. There are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens" (Harris et al, 2007).

ASCO also indicated that "the precise clinical utility and appropriate application for other multi-parameter assays, such as the MammaPrint assay, the so-called Rotterdam Signature, and the Breast Cancer Gene Expression Ratio are under investigation" (Harris et al, 2007).

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, 2016).

Regarding Oncotype DX, ASCO 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 to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.

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)."

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 in 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."

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group

In 2009, the EGAPP the found for Oncotype DX "adequate evidence from one higher quality study to support the association between RS and rates of 10-year distant metastasis, and adequate evidence to support the association between RS and chemotherapy benefit. Study subjects were mainly whites, and how characteristics of other demographic populations might affect test performance is not known" (EGAPP Working Group, 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."

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 Working Group, 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 Working Group, 2016).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Breast Cancer (NCCN, 2018) 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 recommends 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 multigene assays may be considered to help asses risk of recurrence but have not been validated to predict response to chemotherapy”

"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".

The **National Institute for Health and Care Excellence (NICE)** recommends Oncotype DX “as an option for guiding adjuvant chemotherapy decisions for people with estrogen receptor positive (ER+), lymph node negative (LN−) and human epidermal growth factor receptor 2 negative (HER2−) early breast cancer if the person is assessed as being at intermediate risk and information on the biological features of the cancer provided by Oncotype DX is likely to help in predicting the course of the disease and would therefore help when making the decision about prescribing chemotherapy” (NICE, 2013).

NICE also indicates that “MammaPrint, IHC4 and Mammostrat are only recommended for use in research in people with ER+, LN− and HER2− early breast cancer, to collect evidence about potentially important clinical outcomes and to determine the ability of the tests to predict the benefit of chemotherapy. The tests are not recommended for general use in these people because of uncertainty about their overall clinical benefit and consequently their cost effectiveness” (NICE, 2013).

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81479, 81518, 81519, 81520, 81521, 81522, 81599, 84999, 88360, 88361, 88367, 88368, 88381, S3854

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Medical Director review 8/2019

Specialty Matched Consultant Advisory Panel 3/2020

Medical Director review 3/2020

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Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will provide coverage for gene expression testing for breast cancer prognosis when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)

10/1/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Under "When Covered" section 1: reordered and reworded bullets. Previous bullets A-I are now A-F. Deleted the coding table in Billing/Coding section as well as deleted CPT code 81400, and PLA code 00081. Added Related Policies section. Medical Director review 8/2019. (lpr)

10/1/19 Policy statement revised to read: BCBSNC will provide coverage for gene expression testing for breast cancer prognosis when it is determined the medical criteria and guidelines below are met. Wording revised in When Covered section. "Medically Necessary" changed to "Reimbursement is allowed…" Wording revised in the Not Covered section. "Not Medically Necessary" changed to read "Reimbursement is not allowed…" Notification given 10/1/2019 for effective date 12/2/2019. (an)

10/15/19 Wording in When Covered section changed from "Reimbursement is allowed…" to "is considered Medically Necessary." Item 2 revised to read: Use of EndoPredict or PAM50 (Prosigna), to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in women with primary, invasive breast cancer with the same characteristics as considered for Oncotype DX (1A– 1I); with one exception—for individuals with 1-3 involved ipsilateral axillary lymph nodes the tests are considered investigational). Wording in the When Not Covered section changed from "Reimbursement is not allowed…" to "is considered Investigational." Item 2 moved from this section to the revised statement in Item 2 above. Following statement is corrected to read: Use of gene expression assays in men are considered investigational. **Policy remains on notice for effective date 12/10/2019**. (an)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

12/31/19	Added CPT code 81522 to Billing/Coding section for effective date 1/1/2020. (lpr)
2/11/20	Reviewed by Avalon Q4 2019 CAB. No changes to the policy. (lpr)
3/31/20	Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (lpr)
5/1/20	Reviewed by Avalon 1st Quarter 2020 CAB. Clarified When covered section 1→F to include pT1. Temporary expansion of benefit related to COVID-19 pandemic. (lpr)
6/2/20	Temporary expansion of benefit related to COVID-19 pandemic extended through July 31, 2020. We will reevaluate if an additional extension is needed as we approach July 31. (eel)
7/30/20	Temporary expansion of benefit related to COVID-19 pandemic extended through September 30, 2020. We will reevaluate if an additional extension is needed as we approach September 30. (eel)
9/29/20	Temporary expansion of benefit related to COVID-19 pandemic extended through December 31, 2020. We will reevaluate if an additional extension is needed as we approach December 31. (eel)
11/20/20	Temporary expansion of benefit related to COVID-19 pandemic extended through June 30, 2021. We will reevaluate if an additional extension is needed as we approach June 30. (eel)
4/6/21	Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr)