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Subject: Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions | Related Guidelines | Other | References | Updates

DESCRIPTION:

Laboratory tests have been developed to detect the expression, via messenger RNA, of different genes in breast tumor tissue and combine the results to determine prognosis in patients with breast cancer. Test results may help providers and patients decide whether to include adjuvant chemotherapy in the management of breast cancer, to alter treatment in patients with ductal carcinoma in situ or triple-negative (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2) breast cancer (TNBC), or to recommend extended endocrine therapy in patients who are recurrence-free at 5 years.

Summary and Analysis of Evidence: The evidence for individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay) includes multiple prospective clinical trials and prospective-retrospective studies. Patients classified as low-risk with Oncotype DX have a low risk of recurrence in which avoidance of adjuvant chemotherapy is reasonable (average risk at 10 years, 3%-7%; upper bound of the 95% confidence interval [CI], 6%to 10%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 3 prospective-retrospective studies and observational studies. The studies revealed that a low score was associated with a low absolute risk of 10-year distant recurrence (average risk at 10 years for the 2 larger studies, 3%-6%; upper bound of the 95% CI, 6% to 9%). The evidence is sufficient to determine that the technology results in an improvement in the net health

outcome. For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the Breast Cancer Index, the evidence includes findings from 2 prospective-retrospective studies and a registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk Breast Cancer Index score is associated with low 10-year distant recurrence rates (average risk at 10 years, 5%-7%; upper bound of the 95% CI, 8% to 10%). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a prospective-retrospective study and a randomized controlled trial providing evidence for clinical utility. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Prosigna, the evidence includes 2 prospective-retrospective studies evaluating the prognostic ability of Prosigna. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes a clinical utility study demonstrating that postmenopausal women with a RS score of 0 to 25 could safely forego adjuvant chemotherapy without compromising invasive disease–free survival or distant relapse–free survival. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 2 prospective-retrospective analyses. In 1 study, the 10-year distant recurrence rate in low-risk EndoPredict score patients was estimated to be 5% (95% CI, 1% to 9%). In the other study, the 10-year distant recurrence rate in low-risk EndoPredict score patients was estimated to be 5% but the upper bound of the 95% CI was close to 20%. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with MammaPrint (70-gene signature), the evidence includes a clinical utility study. The randomized controlled trial Microarray In Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy showed 5-year distance recurrence rates below the 10% threshold among node-positive (1 to 3 nodes) patients identified as low-risk. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-positive invasive breast cancer who are considering adjuvant chemotherapy who receive gene expression profiling with the Prosigna risk of recurrence (ROR) score, the evidence includes a single prospective-retrospective study. The 10 year distant recurrence rate in low-risk Prosigna ROR patients with a single positive node is roughly twofold the rate in low-risk ROR score node-negative patients. However, in the single available study, the upper bound of the 95% CI for 10-year distant recurrence in node-positive patients classified as ROR score low-risk was about 13%, which approaches the range judged clinically informative in node-negative patients. The predicted recurrence rates require replication. To establish that the test has the potential for clinical utility, it should be able to identify a low-risk group with a recurrence risk that falls within a range that is clinically meaningful for decision-making about avoiding adjuvant chemotherapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have DCIS

considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS Score, the evidence includes a prospective-retrospective study and a retrospective cohort study. Although the studies have shown that the test stratifies patients into high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in patients identified with a Breast DCIS Score is low enough to consider changing the management of DCIS. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have DCIS considering radiotherapy who receive gene expression profiling with DCISionRT, the evidence includes retrospective validation studies. Conclusions are also limited because there are no comparison recurrence estimates for women based on the standard of care (risk predictions based on clinical algorithms).The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with Oncotype DX (21-gene assay), the evidence includes 2 studies using data from the same previously conducted clinical trial. One analysis did not provide CIs and the other study reported a distant recurrence rate of 4.8% (95% CI, 2.9% to 7.9%) for the low-risk group. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have early-stage node-negative invasive breast cancer who are distant recurrence-free at 5 years who are considering extending endocrine treatment who receive gene expression profiling with EndoPredict, the evidence includes 2 analyses of archived tissue samples from 2 previously conducted clinical trials. The studies showed low distant recurrence rates in patients classified as low-risk with EndoPredict. The ability of the test to reclassify patients assessed with a clinical prediction tool was not reported although one publication reported that EPclin was prognostic after controlling for a clinical prediction tool. Additional prospective trials or retrospective-prospective studies of archived samples are needed to confirm risk of disease recurrence with sufficient precision in both low- and high-risk groups. More importantly, clarity is needed about how the test would inform clinical practice. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For individuals who have TNBC considering neoadjuvant chemotherapy who receive gene expression profiling with the Insight TNBCtype test, the evidence includes retrospective cohort studies. Although the studies have shown that TNBC subtypes may differ in their response to neoadjuvant chemotherapy, as the studies were not prospectively designed or powered to specifically address the TNBC population or their specific therapeutic questions, conclusions cannot be drawn based on these findings. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For individuals with breast cancer who receive multiple (repeat) assays of genetic expression in tumor tissue to determine prognosis for a single decision, the evidence includes studies comparing different tests in groups of individuals but no direct evidence evaluating repeat testing with the same test or a combination of tests performed on the same individual. Additionally, clinical practice guidelines recommend against a strategy of repeat testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with BluePrint (80-gene expression assay) in conjunction with MammaPrint or alone, the evidence includes a few observational studies with no direct evidence that BluePrint improves the net health outcome. Clinical utility of BluePrint is unknown; it is unclear how the test will add to treatment

decision making using currently available, accepted methods (eg, clinical and pathologic parameters). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

POSITION STATEMENT:

Note: Coverage may be governed by state or federal mandates.

The use of the 21-gene reverse transcriptase-polymerase chain reaction (PT-PCR) assay (i.e., Oncotype DX®) to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy **meets the definition of medical necessity** in members with newly diagnosed (6 months or less) primary, invasive, **node-negative** breast cancer meeting **ALL** of the following criteria:

- Unilateral tumor;
- Node-negative (lymph nodes with micrometastases (≤ 2 mm in size) are considered node negative) **OR** with 1-3 involved ipsilateral axillary lymph nodes;
- Hormone receptor-positive (ER-positive or PR-positive);
- HER2-negative;
- Tumor size > 0.5 cm;
- The test result will determine if adjuvant chemotherapy or hormonal therapy will be used; **AND**
- The test is ordered by the treating physician.

Use of EndoPredict™, the Breast Cancer Index™, MammaPrint®, or Prosigna™ (also known as PAM50) to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy **meets the definition of medical necessity** in members with primary, invasive, **node-negative** breast cancer that meet the above criteria for for Oncotype DX.

The use of Oncotype Dx to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy **meets the definition of medical necessity** in members with primary, invasive, **node positive** breast cancer meeting all of the following characteristics:

- Postmenopausal (defined as previous bilateral oophorectomy or more than 12 months since the last menstrual period and no previous hysterectomy);
- Unilateral tumor;
- Hormone receptor-positive (ER-positive or PR-positive);
- HER2-negative;
- Stage T1, T2, or operable T3 at high clinical risk of recurrence*;
- 1-3 positive nodes;
- No distant metastases;
- The test result will determine if adjuvant chemotherapy or hormonal therapy will be used;

- When ordered within 6 months after diagnosis; AND
- The test is ordered by the treating physician.

The use of the MammaPrint assay to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy **meets the definition of medical necessity** in members with primary, invasive, **node-positive** breast cancer meeting **ALL** of the following characteristics:

- Unilateral tumor;
- 1-3 positive nodes;
- No distant metastases;
- Hormone receptor-positive (ER-positive or PR-positive);
- HER2-negative;
- Stage T1, T2, or operable T3 at high clinical risk of recurrence*;
- The test result will determine if adjuvant chemotherapy or hormonal therapy will be used;
- When ordered within 6 months after diagnosis; AND
- The test is ordered by the treating physician.

*Tumor Grade	Nodes	Tumor Size
Well differentiated	1-3	≤2 cm or 2.1-5 cm
Moderately differentiated	1-3	Any size
Poorly differentiated or undifferentiated	1-3	Any size

The use of the Breast Cancer Index (BCI) assay to assist in decision of extending adjuvant hormonal therapy beyond 5 years of treatment **meets the definition of medical necessity** for members currently receiving adjuvant hormonal therapy and meeting **ALL** of the following criteria:

- Diagnosed with early-stage breast cancer
- Hormone receptor-positive (ER-positive or PR-positive);
- HER2-negative;
- Node-negative (lymph nodes with micrometastases (≤ 2 mm in size) are considered node negative) OR with 1-3 involved ipsilateral axillary lymph nodes;
- No evidence of distant breast cancer metastasis (i.e., non-relapsed);
- The test result will guide the decision regarding extended adjuvant hormonal therapy; AND
- The test is ordered by the treating physician.

The use of Oncotype Dx to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in **premenopausal** members (defined as less than 6 months since the last menstrual period) with primary, invasive, node positive breast cancer is considered **experimental or investigational**. The evidence is insufficient to permit conclusions on efficacy and net health outcomes.

The use of EndoPredict, the Breast Cancer Index, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy in members with primary, invasive, **node positive** breast cancer is considered **experimental or investigational**. The evidence is insufficient to permit conclusions on efficacy and net health outcomes.

All other indications for the 21-gene PT-PCR assay (i.e., Oncotype DX), EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna are considered **experimental or investigational.** There is a lack of clinical data in peer-reviewed literature to permit conclusions on safety, efficacy and net health outcomes.

Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in members with noninvasive ductal carcinoma in situ (i.e., Oncotype DX® DCIS Score) to inform treatment planning following excisional surgery is considered **experimental or investigational**. The evidence is insufficient to permit conclusions on efficacy and net health outcomes.

All other gene expression assays (e.g., Mammostrat®, BreastOncPx™, Insight® DX Breast Cancer Profile, NexCourse® Breast IHC4, BreastPRS™, MapQuant Dx™, and BreastOncPx™) are considered **experimental or investigational.** The evidence is insufficient to permit conclusions on efficacy and net health outcomes.

The use of Insight TNBCtype to aid in making decisions regarding chemotherapy in members with triple-negative breast cancer is considered **experimental or investigational**. The evidence is insufficient to permit conclusions on efficacy and net health outcomes.

Use of the DCISionRT® assay for predicting recurrence risk in members with noninvasive ductal carcinoma in situ to inform treatment planning after excisional surgery is considered **experimental or investigational**. The evidence is insufficient to permit conclusions on efficacy and net health outcomes.

The following are considered **experimental or investigational** as the evidence is insufficient to permit conclusions on efficacy and net health outcomes:

- The use of gene expression assays to molecularly subclassify breast cancer (eg, BluePrint®)
- The use of gene expression assays for quantitative assessment of ER, PR and HER2 overexpression (eg, TargetPrint®)
- The use of testing to predict response to specific chemotherapy regimens
- Repeat testing, use of more than one test for the same tumor, or testing of multiple tumor sites in the same member.

BILLING/CODING INFORMATION:

CPT Coding:

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)
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)
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)
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)
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)
81523	Oncology (breast), 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
0045U	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 (**Investigational**) (DCIS Score)
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 **(Investigational)**
0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a recurrence risk score (**Investigational**) (DCISionRT)

HCPCS Coding:

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

ICD-10 Diagnosis Codes That Support Medical Necessity:

C50.011-C50.929	Malignant neoplasm of breast
D05.00-D05.92	Lobular carcinoma in situ of breast
Z17.0	Estrogen receptor positive status [ER+]

REIMBURSEMENT INFORMATION:

Reimbursement is subject to post-service medical review. The following information is required documentation to support medical necessity: physician history and physical, pathology report, treating physician visit notes that include documentation that the intention to treat or not treat with adjuvant chemotherapy was contingent, at least in part, on the results of the test for the individual patient in question.

LOINC Codes:

DOCUMENTATION TABLE	LOINC CODES	LOINC TIME FRAME MODIFIER CODE	LOINC TIME FRAME MODIFIER CODES NARRATIVE
Physician history and physical	28626-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Attending physician visit note	18733-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Pathology Reports Sections	26439-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Pathology Study Reports	27898-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products:

The following Local Coverage Determination (LCD) reviewed on the last guideline reviewed date: Molecular Pathology Procedures L34519 located at fcso.com.

The following article was reviewed on the last guideline reviewed date: Billing and Coding: Molecular Pathology and Genetic Testing A58918 located at fcso.com.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Adjuvant chemotherapy: chemotherapy given in addition to surgical therapy, in order to reduce the risk of local or systemic relapse.

ER-positive (estrogen receptor positive): Describes cells that have a protein to which the hormone estrogen will bind. Cancer cells that are ER-positive need estrogen to grow, and may stop growing when treated with hormones that block estrogen from binding.

Estrogen receptor: receptor for estrogens; it's presence conveys a better prognosis for breast cancers.

Gene expression: the detectable effect of a gene.

HER2 (human epidermal growth factor receptor 2): A protein involved in normal cell growth. It is found in high levels on some breast cancer cells.

Micrometastasis: small numbers of cancer cells that have spread from the primary tumor to other parts of the body and are too few to be picked up in a screening or diagnostic test.

Node-negative: being or having cancer that has not spread to nearby lymph nodes.

PR-positive (progesterone receptor positive): Describes cells that have a protein to which the hormone progesterone will bind. Cancer cells that are PR-positive need progesterone to grow and will usually stop growing when treated with hormones that block progesterone from binding.

Stage T1: The tumor is 20 millimeters (mm) or smaller in size at its widest area.

Stage T2: The tumor is larger than 20 mm but not larger than 50 mm.

Stage T3: The tumor is larger than 50 mm.

RELATED GUIDELINES:

Genetic Testing, 05-82000-28

Tumor/Genetic Markers, 05-86000-22

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 01/22/26.

GUIDELINE UPDATE INFORMATION:

10/15/05	New Medical Coverage Guideline.
01/01/06	Annual HCPCS coding update: added code S3854.
09/15/06	Annual review: continue investigational status.

11/15/07	Annual review: position statements changed, description section updated, definitions section updated, guideline reformatted, references updated.
02/15/08	Revised position statement; updated description section, definition section and references.
01/01/09	Annual review: no change to position statements, description section and references updated.
11/15/09	Annual review: position statements updated; description section and references updated.
09/15/10	Annual review: position statements maintained and references updated.
11/15/10	Revision; formatting changes and Program Exceptions section updated.
08/15/11	Scheduled review; position statements maintained and references updated; formatting changes.
03/15/12	Revision; position statement updated; formatting changes.
10/15/12	Annual review; position statements maintained and references updated.
11/01/12	Remove CMN; formatting changes.
05/30/13	Revision; Program Exceptions section and references updated.
11/15/13	Annual review; position statements, program exception, and references updated; formatting changes.
07/01/14	Quarterly HCPCS update. Added code 0008M.
10/15/14	Annual review; position statement section, program exception section, and references updated; formatting changes.
01/01/15	Annual HCPCS/CPT update. Added code 81519.
11/15/15	Annual review; position statement, program exception, and references updated; formatting changes.
01/01/16	Annual HCPCS/CPT update; code S3854 deleted.
07/01/16	Quarterly HCPCS/CPT update. Added code S3854 (code reinstated).
02/15/17	Revision; description, position statements, and references updated; formatting changes.
01/01/18	Annual CPT/HCPCS update. Added codes 81520, 81521; deleted code 0008M.
03/15/18	Review; position statements maintained; description section, coding, and references updated.
07/01/18	Quarterly CPT/HCPCS update. Added code 0045U.
12/15/18	Revision; MammaPrint added to list of tests meeting the definition of medical necessity for specific indications; investigational for all others; coding, program exception, and references updated.
01/01/19	Annual CPT/HCPCS coding update. Added code 81518.
02/15/19	Revision; Coding section, program exception section, and references updated.
11/15/19	Review; Position statements maintained and references updated.
01/01/20	Annual CPT/HCPCS coding update. Added codes 81522 & 0153U.
02/15/20	Revision; MammaPrint position statement added; references updated.
10/15/20	Revision; 21-gene reverse transcriptase-polymerase chain reaction (PT-PCR) assay position statement updated.
02/15/21	Review; Position statements and references updated.

05/15/21	Revision; Position statement for the use of BCI assay to assist in decision of extending adjuvant hormonal therapy added; references updated.
01/01/22	Annual CPT/HCPCS coding update. Code 81523 added.
03/15/23	Review: position statements and references updated.
06/15/23	Revision: Note added to the position statement section.
02/15/24	Review: Position statements maintained, program exception and references updated.
05/15/24	Revision: Position statements and description updated.
02/15/25	Review: Position statements maintained; description and references updated.
02/15/26	Annual review: Position statements maintained.