05-86000-26

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

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DESCRIPTION:

An important part of treatment planning for patients with breast cancer involves determining which patients could benefit from adjuvant cytotoxic chemotherapy. For example, for patients with early-stage, invasive breast cancer (ie, cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of patients' baseline prognosis. However, the absolute benefit of chemotherapy depends on the underlying or baseline risk of recurrence. Patients with the best prognosis have tumors that are small, early-stage, estrogen receptor–positive, and are lymph node–negative. Patients may have received no adjuvant treatment, or adjuvant tamoxifen and/or adjuvant chemotherapy.These patients have an approximately 15% 10-year risk of recurrence with tamoxifen alone, which means that approximately 85% of these patients could avoid the toxicity of adjuvant cytotoxic chemotherapy if they could be accurately identified. Conventional risk classifiers estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and number of affected lymph nodes. Consensus guidelines for defining receptor status exist, however, no single classifier is considered a criterion standard. As a result, more patients are treated with chemotherapy who fail to benefit. Better predictors of recurrence risk could help patient's decision making, some who may prefer to avoid chemotherapy if assured that their risk is low.

Laboratory tests have been developed that 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 postsurgical management of breast cancer, to alter treatment in patients with ductal carcinoma in situ (DCIS), 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.

POSITION STATEMENT:

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 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;
- Who have had surgery and full pathological examination of the tumor completed;
- 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®, and 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 breast cancer that meet the above criteria for for Oncotype DX.

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 breast cancer meeting **ALL** of the following characteristics:

- Unilateral tumor;
- 1-3 positive nodes;
- 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;
- Who have had surgery and full pathological examination of the tumor completed;
- 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.

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.

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)
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)**

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 were reviewed on the last guideline reviewed date: MolDX LCDs located at palmettogba.com.

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 & Coverage Committee on 04/22/21.

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.