Gene Expression Profiling for Managing Breast Cancer Treatment

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<th>Type: Medical Necessity and Investigational / Experimental</th>
<th>Policy Specific Section: Laboratory/Pathology</th>
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<tbody>
<tr>
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**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Description**

For women with early-stage breast cancer, adjuvant chemotherapy provides the same proportional benefit regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk of recurrence. Laboratory tests have been developed that detect the expression, via messenger RNA (mRNA) or protein, of many different genes in breast tumor...
tissue and combine the results into a prediction of distant recurrence risk for women with early-stage breast cancer. Test results may help providers and patients decide whether to include adjuvant chemotherapy in postsurgical management. For example, women with the best prognosis have small tumors, are estrogen receptor-positive, and lymph node-negative.

Conventional risk classifiers estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. However, no single classifier is considered a gold standard and several common criteria have qualitative or subjective components that add variability to risk estimates. As a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help women, who prefer to avoid chemotherapy if assured that their risk is low, make better treatment decisions in consultation with their physicians.

Policy

The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay, Oncotype DX®, to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy may be considered medically necessary in individuals with breast cancer meeting all of the following characteristics:

- Recently diagnosed within the past 6 months
- Unilateral tumor and one of the following:
  - Tumor size 0.6-1 cm with moderate/poor differentiation
  - Tumor size 0.6-1 cm with unfavorable features (e.g., angiolymphatic invasion, high histologic grade, or high nuclear grade) (See Policy Guideline)
  - Tumor size greater than 1 cm
- Hormone receptor positive (estrogen receptor [ER]-positive or progesterone receptor [PR]-positive)
- Human epidermal growth factor receptor 2 (HER2) negative
- Node negative (lymph nodes with micrometastases less than 2 mm in size are considered node negative for this policy statement)
- When the test will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option)

The use of the 21-gene RT-PCR assay, Oncotype DX®, for tumors less than 0.6 cm in size is considered not medically necessary.

All other indications for the 21-gene RT-PCR assay, Oncotype DX®, including determination of recurrence risk in breast cancer patients with positive lymph nodes greater than 2 mm or patients with bilateral disease, are considered investigational.

Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (DCIS), Oncotype DX® DCIS, to inform treatment planning following excisional surgery, is considered investigational.
Other gene expression assays for any indication are considered investigational, including, but not limited to:

- MammaPrint®
- Breast Cancer IndexSM
- Mammostrat®
- BreastOncPx™
- PAM50 Breast Cancer Intrinsic Classifier
- NexCourse® Breast IHC4

**Policy Guideline**

**High Grade Tumor**

High histologic grade (differentiation) refers to how well the tumor cells resemble normal cells of the same type of tissue (e.g., surrounding breast tissue). Poor or undifferentiated cells are considered high grade and do not resemble normal breast tissue cells. Well-differentiated cells are considered low grade and more closely resemble normal breast tissue cells. High nuclear grade refers to the size and shape of the nucleus in the tumor cells and a percentage of cells that are dividing.

Breast cancer, though rare, can occur in males and the pathology is similar to females. The American Cancer Society (2012) states, “Because there have been few clinical trials on treatment of male breast cancer, most doctors base their treatment recommendations on their experience with the disease and on the results of studies of breast cancer in women. With some minor variations, breast cancer in men is treated the same way as breast cancer in women.”

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). The test should be ordered in the context of a physician-patient discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.

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.

Eight gene expression tests are commercially available in the United States:

- Oncotype DX® (a 21-gene reverse transcriptase-polymerase chain reaction [RT-PCR] assay; Genomic Health, Inc., Redwood City, CA)
- Oncotype DX® DCIS (assay that is obtained by an algorithm containing 12 genes that are generated from the Oncotype DX 21-gene assay; Genomic Health, Inc., Redwood City, CA)
- 70-gene signature MammaPrint® (Agendia, Irvine, CA)
- Breast Cancer Index\textsuperscript{SM}, a combination of the Molecular Grade Index (MG\textsubscript{I}\textsuperscript{SM}) and the HOXB13:IL17BR Index (H/I\textsubscript{ISM}) (bioTheranostics, Inc., San Diego, CA)
- Mammostrat\textsuperscript{\textregistered} (Clariant Diagnostic Services, Aliso Viejo, CA)
- BreastOncPx\textsuperscript{TM} (Breast Cancer Prognosis Gene Expression Assay; LabCorp, Burlington, NC)
- PAM50 Breast Cancer Intrinsic Classifier (formerly supplied by ARUP Laboratories, Salt Lake City, UT)
- NexCourse\textsuperscript{\textregistered} Breast IHC4 (Genoptix, Inc., Carlsbad, CA)

**Coding**

The following are examples of CPT/HCPCS coding for specific gene expression assays based on manufacturer guidance or laboratories offering the tests.

(Note: Different laboratories may have variance in coding or coding algorithms):

- Oncotype DX\textsuperscript{\textregistered}/Oncotype DX\textsuperscript{\textregistered} DCIS:
  - HCPCS code S3854
- MammaPrint\textsuperscript{\textregistered}:
  - May likely use either of the following:
    - CPT code 84999 (unlisted chemistry procedure) or 81479 (unlisted molecular pathology procedure)
    - HCPCS code S3854
- Breast Cancer Index\textsuperscript{SM}:
  - May likely use an unlisted CPT procedure code such as:
    - 81479 (unlisted molecular pathology procedure)
- Mammostrat\textsuperscript{\textregistered}:
  - CPT code 88399 (unlisted surgical pathology procedure)
- BreastOncPx\textsuperscript{TM}:
  - May likely use an unlisted CPT procedure code such as:
    - 81479 (unlisted molecular pathology procedure)

**Internal Information**

There is an MD Determination Form for this Medical Policy. It can be found on the following Web page:
http://myworkpath.com/healthcareservices/MedicalOperations/PSR_Determination_Pages.htm

**Documentation Required for Clinical Review**

- History and physical and/or consultation notes including:
  - Specific lab test requested
  - Reason for test and whether the test will help guide treatment decision regarding chemotherapy
  - Breast tumor size and classification, node status, differentiation and/or unfavorable features
  - HER2 status
The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.