

## Gene Expression Profiling and Biomarker Testing for Breast Cancer

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### Related Medical Guideline

#### [Gene Expression Profiling](#)

### Definitions

Lab test	Description
<a href="#">Breast Cancer Index (BCI)</a>	Uses polymerase chain reaction (PCR) to interrogate selected proliferation-related and endocrine signaling-related genes, and may identify a subset of postmenopausal women who are at increased risk of late relapses for ER+ breast cancer and who may derive a greater benefit from extended hormone therapy.
<a href="#">EndoPredict®</a>	Gene expression profile of a patient's tumor combined with clinical status of tumor in context with other patient data. The test is used to provide decision-guidance regarding the medical necessity of chemotherapy.
<a href="#">MammaPrint® 70-gene Breast Cancer Recurrence Assay</a>	Qualitative in vitro diagnostic test service using the gene expression profile of fresh breast cancer tissue samples to assess a patients' risk for distant metastasis (up to 10 years for patients less than 61 years old, up to 5 years for patients ≥ 61 years).
<a href="#">Oncotype DX®</a>	Multiparameter gene expression assay that predicts the likelihood of breast cancer recurrence in members with newly diagnosed early stage invasive breast cancer. The test is used to guide use of adjuvant tamoxifen and adjuvant chemotherapy.
<a href="#">Prosigna® Cancer Prognostic Gene Signature Assay</a>	Gene expression profile of a patient's tumor is compared with each of the 4 PAM50 prototypical molecular profiles to determine the degree of similarity. The results, in combination with a proliferation score and tumor size, produce an individualized Risk of Recurrence (ROC) Score.
<a href="#">Urokinase Plasminogen Activator Protein Inhibitor Test</a>	Serological biomarker test — elevated expression levels of urokinase and several other components of the plasminogen activation system are found to be correlated with tumor malignancy.

## Key

Estrogen receptor	Progesterone receptor	Human epidermal growth factor receptor 2	Pathologic
ER	PgR	HER2	pN

## Guideline

Gene expression profiling is considered medically necessary for adjuvant chemotherapy treatment decisions in males or females with recently diagnosed early stage breast cancer.

A pre-test discussion between the provider and member regarding potential results, and agreement that results will be used to guide therapy, must be documented as having been completed.

- A.** Preferred tests — Oncotype DX, EndoPredict\*, Prosigna or urokinase plasminogen activator (uPA) and its plasminogen activator inhibitor type 1 (PAI-1) are considered medically necessary when all of the following are applicable:
1. ER/PgR-positive
  2. HER2-negative
  3. Node-negative — pN0 or pN0(i+) (micrometastases < 0.2 mm in regional lymph nodes) (or 1–3 positive nodes for Oncotype [i.e., member may be node-negative or node-positive when Oncotype is used])

\*Note: EndoPredict is covered for all lines of business. For Medicare members, EndoPredict is covered for the management of post-menopausal women diagnosed with early-stage (TNM stage T1-3, N0-1) estrogen-receptor (ER) positive, Her2-negative breast cancer, who are either lymph node-negative or who have 1–3 positive nodes, and for whom treatment with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors) is being considered.

- B.** MammaPrint is considered medically necessary when all the following are applicable:
1. ER/pgR-positive
  2. HER2-negative
  3. Node negative or 1–3 local lymph nodes
  4. At high clinical risk (per MINDACT trial categorization, as determined by using a modified version of Adjuvant! Online\*)
- C.** HerMark® and Oncotype DX® DCIS are only covered for Medicare members (See Limitations/Exclusions)
- D.** Breast Cancer Index® (BCI) is considered medically necessary when all the following are applicable:
1. Unilateral tumor
  2. Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3)
  3. ER/pgR-positive
  4. HER2-negative
  5. Node-negative or node-positive with 1–3 positive nodes
  6. Adjuvant endocrine systemic chemotherapy is a planned treatment option or results from BCI test will be used for adjuvant chemotherapy treatment decisions

## Limitations/Exclusions

- A. Only one test is covered. Additional testing may be considered medically necessary for members with histologically distinct tumors when the medical necessity criteria for the test to be utilized is met.
- B. Testing for indications other than those listed above (e.g., colon cancer) is not considered medically necessary.
- C. Gene expression profiling using tests other than those listed above are not considered medically necessary due to insufficient evidence of therapeutic value (e.g., Blueprint™, , H:I ratio, Rotterdam/Veridex 76-gene prognostic signature, HOX13:IL17BR [two-gene signature], Mammostrat, TargetPrint)
- D. HerMark is a covered for Medicare members only; see [Local Coverage Article: MolDX: HERmark® Assay by Monogram Update](#).
- E. Oncotype DX DCIS is covered for Medicare members only; see [Local Coverage Determination: MolDX: ONCOTYPE DX® Breast Cancer for DCIS \(Genomic Health™\)](#)

### Revision History

6/10/2022	Added positive-node coverage to Breast Cancer Index test
2/11/2022	Added coverage for Breast Cancer Index test
2/14/2020	Expanded Oncotype indications to include 1–3 positive nodes for Commercial and Medicaid members (previously Medicare only) Removed micrometastases prerequisite language for MammaPrint
3/8/2019	Created preferred test section to denote ASCO endorsements Removed MammaPrint from preferred section to communicate ASCO's position of utility for high clinical risk Removed BCI test from preferred section to denote change of ASCO endorsement to not recommended Added Oncotype DX® DCIS for Medicare members
2/9/2018	Added coverage note for EndoPredict specific to Medicare members
2/10/2017	Added coverage for EndoPredict Added coverage note for Oncotype specific to Medicare members
5/13/2016	Added coverage for Prosigna and urokinase plasminogen activator protein inhibitor testing
12/21/2015	Gene Expression Profiling for Breast Cancer is a new guideline consolidated from the separate BCI, MammaPrint and Oncotype guidelines

### Applicable Procedure Codes

81479	Unlisted molecular pathology procedure
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 (Eff. 01/01/2019)
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
81599	Unlisted multianalyte assay with algorithmic analysis [for EndoPredict]
85415	Fibrinolytic factors and inhibitors; plasminogen activator

S3854	Gene expression profiling panel for use in the management of breast cancer treatment
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### Applicable ICD-10 Diagnosis Codes

C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast



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NCCN Guideline® Breast Cancer. V3.2022. [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). Accessed June 16, 2022.

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