Gene Expression Profiling and Biomarker Testing for Breast Cancer

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Related Medical Guideline

Gene Expression Profiling

Definitions

Lab test	Description
Breast Cancer Index (BCI)	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.
EndoPredict®	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.
MammaPrint® 70-gene Breast Cancer Recurrence Assay	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).
Oncotype DX®	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.

Prosigna® Cancer Prognostic Gene Signature Assay	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.

Key

Estrogen receptor	Progesterone receptor	Human epidermal growth factor receptor 2	Pathologic
ER	**PG R**	**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 or Prosigna are considered medically necessary when all of the following are applicable:

1. Estrogen receptor (ER) or progesterone receptor (PG R) positive
2. Human epidermal growth factor receptor 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])

B. MammaPrint is considered medically necessary when all the following are applicable:

1. ER or PG R 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 for predictive testing for extended endocrine therapy when all the following are applicable:

1. Unilateral tumor
2. Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3)
3. ER or PG R positive
4. HER2-negative
5. Node-negative or micro-metastatic node-positive with 1–3 positive nodes
6. Clinical treatment score post-5 years

Limitations/Exclusions

A. 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

3/14/2025	Removed one-test-only coverage restriction
5/17/2024	Removed note stipulating tumor- classification criteria for the EndoPredict
2/9/2024	Removed the Urokinase-type plasminogen activator test as a preferred test
5/25/2023	Added predictive testing language to Breast Cancer Index section
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
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
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

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

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
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
D05.10	Intraductal carcinoma in situ of unspecified breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.80	Other specified type of carcinoma in situ of unspecified breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.90	Unspecified type of carcinoma in situ of unspecified breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
Z17.0	Estrogen receptor positive status [ER+]
Z17.1	Estrogen receptor negative status [ER-]
Z85.3	Personal history of malignant neoplasm of breast

References

Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. Fabrice Andre, Nofisat Ismaila, Kimberly H. Allison, William E. Barlow, Deborah E. Collyar, Senthil Damodaran, N. Lynn Henry, Komal Jhaveri, Kevin Kalinsky, Nicole M. Kuderer, Anya Litvak, Erica L. Mayer, Lajos Pusztai, Rachel Raab, Antonio C. Wolff, and Vered Stearns. Journal of Clinical Oncology 2022 40:16, 1816-1837.

Noridian Healthcare Solutions. Local Coverage Determination (LCD): MolDX: EndoPredict® Breast Cancer Gene Expression Test (L37295). November 2021. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36941&ver=21&SearchType=Advanced&CoverageSelection=Local&ArticleType=SAD%7cEd&PolicyType=Both&s=All&KeyWord=oncotype&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAACAAgAAA&=. Accessed March 21, 2025.

Noridian Healthcare Solutions. Local Coverage Determination (LCD): MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™). November 2021. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36941&ver=21&SearchType=Advanced&CoverageSelection=Local&ArticleType=SAD%7cEd&PolicyType=Both&s=All&KeyWord=oncotype&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAACAAgAAA&=. Accessed March 21, 2025.

Cardoso F, van't Veer LJ, Bogaerts J, Slaets L, Viale G, Delaloge S, Pierga JY, Brain E, Causeret S, DeLorenzi M, Glas AM, Golfinopoulos V, Goulioti T, Knox S, Matos E, Meulemans B, Neijenhuis PA, Nitz U, Passalacqua R, Ravdin P, Rubio IT, Saghatchian M, Smilde TJ, Sotiriou C, Stork L, Straehle C, Thomas G, Thompson AM, van der Hoeven JM, Vuylsteke P,

Bernards R, Tryfonidis K, Rutgers E, Piccart M; MINDACT Investigators. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med. 2016 Aug 25;375(8):717-29).

NCCN Guideline® Breast Cancer. V3.2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed May 21, 2024.

Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, Ravdin P, Bugarini R, Baehner FL, Davidson NE, Sledge GW, Winer EP, Hudis C, Ingle JN, Perez EA, Pritchard KI, Shepherd L, Gralow JR, Yoshizawa C, Allred DC, Osborne CK, Hayes DF; Breast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol. 2010 Jan;11(1):55-65.

Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, Geyer CE Jr, Dees EC, Goetz MP, Olson JA Jr, Lively T, Badve SS, Saphner TJ, Wagner LI, Whelan TJ, Ellis MJ, Paik S, Wood WC, Ravdin PM, Keane MM, Gomez Moreno HL, Reddy PS, Goggins TF, Mayer IA, Brufsky AM, Toppmeyer DL, Kaklamani VG, Berenberg JL, Abrams J, Sledge GW Jr. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2018 Jul 12;379(2):111-121).

Noordhoek I, Treuner K, Putter H, Zhang Y, Wong J, Meershoek-Klein Kranenbarg E, Duijm-de Carpentier M, van de Velde CJH, Schnabel CA, Liefers GJ. Breast Cancer Index Predicts Extended Endocrine Benefit to Individualize Selection of Patients with HR+ Early-stage Breast Cancer for 10 Years of Endocrine Therapy. Clin Cancer Res. 2021 Jan 1;27(1):311-319. doi: 10.1158/1078-0432.CCR-20-2737. Epub 2020 Oct 27. PMID: 33109739.

Sgroi DC, Carney E, Zarrella E, Steffel L, Binns SN, Finkelstein DM, Szymonifka J, Bhan AK, Shepherd LE, Zhang Y, Schnabel CA, Erlander MG, Ingle JN, Porter P, Muss HB, Pritchard KI, Tu D, Rimm DL, Goss PE. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. J Natl Cancer Inst. 2013 Jul 17;105(14):1036-42. doi: 10.1093/jnci/djt146. Epub 2013 Jun 28. PMID: 23812955; PMCID: PMC3888138.

Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, Duijm-de Carpentier M, Putter H, van den Bosch J, Maartense E, van Leeuwen-Stok AE, Liefers GJ, Nortier JWR, Rutgers EJT, van de Velde CJH; IDEAL Study Group. Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05). J Natl Cancer Inst. 2018 Jan 1;110(1). doi: 10.1093/jnci/djx134. PMID: 28922787.

Bartlett JMS, Sgroi DC, Treuner K, Zhang Y, Ahmed I, Piper T, Salunga R, Brachtel EF, Pirrie SJ, Schnabel CA, Rea DW. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol. 2019 Nov 1;30(11):1776-1783. doi: 10.1093/annonc/mdz289. PMID: 31504126; PMCID: PMC6927322.

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