

DRAFT Medical Coverage Policy | Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer



EFFECTIVE DATE: 01|01|2024

POLICY LAST UPDATED: 10|02|2023

OVERVIEW

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 individuals with breast cancer. Test results may help providers and individuals decide whether to include adjuvant chemotherapy in the postsurgical management of breast cancer, to alter treatment in individuals 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 individuals who are recurrence-free at five years.

The following tests are addressed in this policy:

- Breast Cancer Index (Biotheranostics) (CPT code 81518)
- Oncotype DX Breast (Genomic Health) (CPT code 81519)
- Prosigna (NanoString Technologies) (CPT code 81520)
- MammaPrint (Agendia) (CPT code 81521)
- EndoPredict (Myriad) (CPT code 81522)
- MammaPrint NGS (Agendia) (CPT code 81523)
- Oncotype DX Breast DCIS (Ductal Carcinoma In Situ) Score (Genomic Health) (CPT code 0045U)
- BluePrint (Agendia) (CPT code 81479)
- DCISionRT® (Prelude Corporation) (CPT code 0295U)

MEDICAL CRITERIA

Breast Cancer Index – CPT 81518

The following criteria may be used for Medicare Advantage Plans and Commercial Products.

Breast Cancer Index may be considered medically necessary for members with invasive breast cancer when the following criteria are met:

- Pathology reveals invasive carcinoma of the breast that is ER+ and/or PR+ and HER2-; and
- Patient has early-stage disease (T1-3, pN0-N1, M0); and
- Patient has no evidence of distant breast cancer metastasis (i.e., non-relapsed); and
- Test results will be used in determining treatment management of the patient for chemotherapy and/or extension of endocrine therapy.

Oncotype DX Breast – CPT 81519

The following criteria may be used for Medicare Advantage Plans and Commercial Products.

Oncotype DX Breast may be considered medically necessary for members with the following findings:

- estrogen-receptor positive, node-negative carcinoma of the breast
- estrogen-receptor positive micrometastases of carcinoma of the breast, and
- estrogen-receptor positive breast carcinoma with 1-3 positive nodes.

Prosigna – CPT 81520

The following criteria may be used for Medicare Advantage Plans and Commercial Products.

Prosigna may be considered medically necessary for members either:

- ER+, lymph node-negative, stage I or II breast cancer; or
- ER+, lymph node-positive (1-3 positive nodes), stage II breast cancer.

MammaPrint – CPT 81521

MammaPrint NGS – CPT 81523

The following criteria may be used for Medicare Advantage Plans and Commercial Products.

The use of the MammaPrint assay to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered medically necessary in members with primary, invasive breast cancer meeting all of the following characteristics:

- unilateral tumor;
- hormone receptor-positive (ie, estrogen receptor-positive or progesterone receptor-positive);
- human epidermal growth factor receptor 2-negative;
- stage T1 or T2 or operable T3 at high clinical risk;
- one to three positive nodes (N1);
- no distant metastases;
- who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors);
- eligible for a chemotherapy regimen containing a taxane, an anthracycline, or both;
- when the test result aids the patient in deciding on chemotherapy (ie, when chemotherapy is a therapeutic option); AND
- when ordered within 6 months after diagnosis, because the value of the test for making decisions regarding delayed chemotherapy is unknown.

High clinical risk is defined as:

- Grade: well differentiated; tumor size, 2.1 to 5 cm
- Grade: moderately differentiated; tumor size, any size
- Grade: poorly differentiated or undifferentiated; tumor size, any size

EndoPredict – CPT 81522

The following criteria may be used for Medicare Advantage Plans and Commercial Products.

EndoPredict may be considered medically necessary for members with T1-3, N0-1 breast cancer when the following criteria are met:

- Patient is post-menopausal, and
- Pathology (excisional or biopsy) reveals invasive carcinoma of the breast that is ER-positive, Her2-negative, and
- Patient is either lymph node-negative or has 1-3 positive lymph nodes, and
- Patient has no evidence of distant metastasis, and
- Test result will be used to determine treatment choice between endocrine therapy alone vs. endocrine therapy plus chemotherapy.

Oncotype DX Breast DCIS Score – CPT 0045U

The following criteria may be used for Medicare Advantage Plans and Commercial Products.

The Oncotype DX DCIS assay may be considered medically necessary when the following clinical conditions are met:

- Pathology (excisional or core biopsy) reveals ductal carcinoma in situ of the breast (no pathological evidence of invasive disease), and
- FFPE specimen with at least 0.5 mm of DCIS length, and
- Patient is a candidate for and is considering breast conserving surgery alone as well as breast conserving surgery combined with adjuvant radiation therapy, and
- Test result will be used to determine treatment choice between surgery alone vs. surgery with radiation therapy, and
- Patient has not received and is not planning on receiving a mastectomy.

PRIOR AUTHORIZATION

Medicare Advantage Plans

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products via the online tool for participating providers for the following tests:

- Breast Cancer Index
- EndoPredict
- Oncotype DX Breast
- MammaPrint
- MammaPrint NGS
- Oncotype DX Breast DCIS Score
- Prosigna

Medicare Advantage Plans and Commercial Products

There is no specific CPT coding for some of the services referenced in this policy. Therefore, an Unlisted CPT code should be used (see Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans

The following tests may be considered medically necessary when the medical criteria above are met:

- Breast Cancer Index
- EndoPredict
- MammaPrint
- MammaPrint NGS
- Oncotype DX Breast
- Oncotype DX Breast DCIS Score
- Prosigna

The following test is not covered as the evidence is insufficient to determine the effects of the technology on health outcomes:

- BluePrint
- DCISionRT

Commercial Products

The following tests may be considered medically necessary when the medical criteria above are met:

- Breast Cancer Index
- EndoPredict
- MammaPrint
- MammaPrint NGS
- Oncotype DX Breast
- Oncotype DX Breast DCIS Score
- Prosigna

The following tests are not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes:

- BluePrint
- DCISionRT

For Commercial Products ONLY:

Use of more than one type of test to determine necessity of adjuvant therapy in breast cancer (Breast Cancer Index, OncotypeDx Breast, Prosigna, MammaPrint, EndoPredict, or MammaPrint NGS) is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member’s plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for laboratory tests and applicable not covered/not medically necessary benefits/coverage.

BACKGROUND

Breast Cancer Index

The Breast Cancer Index (BCI) is a molecular assay that evaluates the differential expression (qRT-PCR) of 11 genes: 7 informational genes that interrogate multiple cell-signaling pathways associated with breast cancer recurrence [proliferative (Molecular Grade Index or MGI) and estrogen signaling (HoxB13/IL17BR or H/I)], and 4 RNA normalization (reference) genes. The test provides both prognostic and predictive results reported as 1) individualized risk of DR as a percentage based on a BCI Score. Specific risk estimates are generated for the risk of overall DR (0-10 years after diagnosis) and late DR (5-10 years after diagnosis) in individuals who are recurrence-free at year 5, and 2) the test separately reports a categorical output of H/I High versus Low for likelihood of endocrine response, with a High H/I ratio associated with endocrine responsive disease.

BCI is used for the management of postmenopausal women diagnosed with early-stage (TNM stage T1-3, pN0-N1, M0), non-relapsed, ER and/or PR-positive, HER2-negative breast cancer, who are being treated with primary adjuvant endocrine therapy. The test is used by physicians to provide a genomic-based estimate of distant recurrence risk and endocrine responsiveness to identify individuals:

- who have sufficiently low risk of distant recurrence over 10 years, wherein the absolute benefit of adjuvant chemotherapy is unlikely to outweigh the risks of serious toxicities; and/or

- who are distant recurrence-free and have a sufficiently low residual risk of late distant recurrence (post- 5 years from diagnosis) wherein the absolute benefit of extension of endocrine therapy is unlikely to outweigh the risks of complications and nonadherence to therapy

BCI is tested once per patient lifetime on formalin-fixed, paraffin-embedded (FFPE) tissue from the primary tumor specimen obtained prior to adjuvant treatment.

Oncotype DX Breast

Oncotype Dx (Genomic Health, Inc., Redwood City, CA) is a diagnostic laboratory-developed assay that quantifies the likelihood of breast cancer recurrence in women with newly diagnosed, stage I or II, node negative, estrogen receptor positive breast cancer, who will be treated with tamoxifen. The assay analyzes the expression of a panel of 21 genes and is intended for use in conjunction with other conventional methods of breast cancer analysis. Together with staging, grading, and other tumor marker analyses, Oncotype Dx is intended to provide greater insight into the likelihood of systemic disease recurrence.

Prosigna

Prosigna is intended for use as a prognostic indicator in conjunction with other clinicopathologic factors for distant recurrence-free survival at 10 years in postmenopausal women with hormone receptor (HR)-positive, lymph node-negative/stage I or II, or lymph node-positive (1-3 positive nodes)/stage II breast cancer to be treated with adjuvant endocrine therapy alone. The assay measures the expression profiles of genes included in the PAM50 gene signature, as well as 8 housekeeping genes (for normalization), 6 positive controls and 8 negative controls.

MammaPrint® and MammaPrint® NGS

MammaPrint is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the gene expression profile of FFPE breast cancer tissue samples to assess an individual's risk for distant metastasis.

MammaPrint® NGS is applied to breast cancer tissue from breast cancer specimens to measure the 70 content genes and apply the same algorithm to those genes which is reported as an index related to the risk of distant metastases of breast cancer.

EndoPredict®

EndoPredict® is intended for use in FFPE breast tumor tissue from postmenopausal women diagnosed with early-stage (TNM stage T1-3, N0-1) 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 (eg, tamoxifen or aromatase inhibitors) is being considered. The test is used by physicians in the management of early-stage breast cancer by identifying those individuals with a low-risk EPclin score, for whom the absolute benefit of adjuvant chemotherapy is unlikely to outweigh the risks.

Note: The EndoPredict® test should not be ordered if a physician does not intend to act upon the test result.

Oncotype DX Breast DCIS Score

The DCIS Score is an RNA based assay measuring the expression of five proliferation genes, progesterone receptor (PR), GSTM1 and five reference genes (Figure 1) with results reported as a numerical score along with accompanying interpretive information. The assay is performed on formalin fixed paraffin-embedded (FFPE) tissue blocks containing DCIS. The DCIS Score was developed based upon analyses of multiple correlative science studies comparing gene expression profiles between invasive and DCIS tumor samples. An algorithm was developed using scaling and category cut-points based on the analysis of the DCIS Score result in a separate cohort of DCIS individuals.

BluePrint

Molecular subtyping profile or Blueprint is proposed for the evaluation of an individual's prognosis when diagnosed with breast cancer. The multigene profile classifies breast cancer into basal type, luminal type and ERBB type (HER2/neu positive) molecular subclasses to stratify an individual's risk to purportedly assist with treatment decisions. Aetna Agendia Blueprint has an 80-gene profile that classifies breast cancer into molecular subtypes. The profile separates tumors into Basal-type, Luminal-type and ERBB2-type subgroups by measuring the functionality of downstream genes for each of these molecular pathways to inform the physician of the potential effect of adjuvant therapy.

There is insufficient evidence to support the required clinical utility for Blueprint. The evidence is insufficient to determine the effects of the technology on health outcomes.

DCISionRT

The DCISionRT combines 7 monoclonal protein markers (COX-2, FOXA1, HER2, Ki-67, p16/INK4A, PR, and SIAH2) assessed in tumor tissue with 4 clinicopathologic factors (age at diagnosis, tumor size, palpability, and surgical margin status) to produce a score that stratifies individuals with DCIS into 3 risk groups: low risk, elevated risk with good response, and elevated risk with poor response. The purpose of the test is to predict radiation benefit in individuals with DCIS following breast conserving surgery.

For individuals who have DCIS considering radiotherapy who receive gene expression profiling with DCISionRT, the evidence includes retrospective validation studies. One Simon et al (2009) category B study provided evidence for clinical validity which showed no benefit of radiation therapy among a group of participants classified as low risk using the DCIS RT score at a threshold of <3 (absolute risk difference for invasive recurrence 1.2% (-5.7% to 8.2%). However, it is unclear whether the estimated 10-year recurrence risk for this group (12.4%; 95% CI 7.2% to 20.8% for invasive recurrence) is low enough to consider changing management or is estimated with sufficient precision. 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.

CODING

The following CPT code(s) may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria identified above are met:

This code can be used for Breast Cancer Index:

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

This code can be used for Oncotype DX Breast:

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

This code can be used for Prosigna:

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

This code can be used for MammaPrint:

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

This code can be used for EndoPredict:

81522 Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score

This code can be used for MammaPrint NGS:

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

This code can be used for Oncotype DX Breast DCIS (Ductal Carcinoma In Situ) Score:

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

The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products.

This code can be used for DCISionRT:

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

The following CPT code requires prior authorization for Medicare Advantage Plans and Commercial Products. The code can be used for any test identified in this policy that does not have a specific CPT code.

81479 Unlisted molecular pathology procedure

RELATED POLICIES

Biomarker Testing Mandate

Genetic Testing Services

Medical Necessity

Proprietary Laboratory Analyses (PLA)

Unlisted Procedures

PUBLISHED

Provider Update, February 2023, November 2023

Provider Update, February 2022

Provider Update, September 2021

Provider Update, June 2021

Provider Update, June 2020

REFERENCES

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Breast Cancer Index™ (BCI) Gene Expression Test (L37822)
2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Breast Cancer Index™ (BCI) Gene Expression Test (A57773)
3. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35160)
4. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Oncotype DX® Breast Cancer Assay (A54480)
5. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Breast Cancer Assay: Prosigna® (L36386)
6. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Breast Cancer Assay: Prosigna (A57364)

7. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): Breast Cancer Assay: Prosigna® (L363864)
8. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Breast Cancer Assay: Prosigna® (A573643)
9. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: MammaPrint (A54445)
10. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: ENDOPREDICT® Breast Cancer Gene Expression Test (L37295)
11. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: ENDOPREDICT® Breast Cancer Gene Expression Test (A576078)
12. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: EndoPredict® Breast Cancer Gene Expression Test (L37295)
13. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Billing and Coding: MolDX: EndoPredict® Breast Cancer Gene Expression Test (A57607)
14. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™) (L36941)
15. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™) (A57619)
16. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35025)
17. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT) (A56853)
18. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: BLUEPRINT® Test (A55115)
19. Colleoni M, Sun Z, Price KN, et al. Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V. *J Clin Oncol.* Mar 20 2016; 34(9): 927-35. PMID 26786933
20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed September 13, 2022.
21. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol.* Aug 10 2010; 28(23): 3784-96. PMID 20625130
22. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. *J Clin Oncol.* Jul 20 2014; 32(21): 2255-69. PMID 24868023
23. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol.* Mar 10 2008; 26(8): 1275-81. PMID 18250347
24. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol.* Nov 01 2013; 31(31): 3997-4013. PMID 24101045
25. Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet.* Aug 27 2011; 378(9793): 771-84. PMID 21802721
26. Tormey DC, Gray R, Falkson HC. Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group. *J Natl Cancer Inst.* Dec 18 1996; 88(24): 1828-33. PMID 8961972
27. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst.* May 02 2001; 93(9): 684-90. PMID 11333290

28. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. *J Natl Cancer Inst.* Mar 21 2001; 93(6): 456-62. PMID 11259471
29. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet.* Mar 09 2013; 381(9869): 805-16. PMID 23219286
30. Gray RG, Rea D, Handley K, et al. aT^oTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [abstract]. *J Clin Oncol.* 2013;31(18 Suppl):5-5.
31. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst.* Dec 19 2007; 99(24): 1845-53. PMID 18073378
32. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med.* Nov 06 2003; 349(19): 1793-802. PMID 14551341
33. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst.* Sep 07 2005; 97(17): 1262-71. PMID 16145047
34. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol.* Apr 20 2008; 26(12): 1965-71. PMID 18332472
35. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. *Lancet Oncol.* Nov 2017; 18(11): 1502-1511. PMID 29031778
36. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal Duration of Extended Adjuvant Endocrine Therapy for Early Breast Cancer; Results of the IDEAL Trial (BOOG 2006-05). *J Natl Cancer Inst.* Jan 01 2018; 110(1). PMID 28922787
37. Khosrow-Khavar F, Filion KB, Al-Qurashi S, et al. Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Ann Oncol.* Mar 01 2017; 28(3): 487-496. PMID 27998966
38. Amir E, Seruga B, Niraula S, et al. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst.* Sep 07 2011; 103(17): 1299-309. PMID 21743022
39. Tseng OL, Spinelli JJ, Gotay CC, et al. Aromatase inhibitors are associated with a higher fracture risk than tamoxifen: a systematic review and meta-analysis. *Ther Adv Musculoskelet Dis.* Apr 2018; 10(4): 71-90. PMID 29619093
40. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst.* Nov 04 2009; 101(21): 1446-52. PMID 19815849
41. Kelly CM, Krishnamurthy S, Bianchini G, et al. Utility of oncotype DX risk estimates in clinically intermediate risk hormone receptor-positive, HER2-normal, grade II, lymph node-negative breast cancers. *Cancer.* Nov 15 2010; 116(22): 5161-7. PMID 20665886
42. Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet.* Feb 04 2012; 379(9814): 432-44. PMID 22152853
43. Pauker SG, Kassirer JP. Therapeutic decision making: a cost-benefit analysis. *N Engl J Med.* Jul 31 1975; 293(5): 229-34. PMID 1143303
44. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *N Engl J Med.* May 15 1980; 302(20): 1109-17. PMID 7366635
45. Simes RJ, Coates AS. Patient preferences for adjuvant chemotherapy of early breast cancer: how much benefit is needed?. *J Natl Cancer Inst Monogr.* 2001; (30): 146-52. PMID 11773309
46. Duric VM, Stockler MR, Heritier S, et al. Patients' preferences for adjuvant chemotherapy in early breast cancer: what makes AC and CMF worthwhile now?. *Ann Oncol.* Nov 2005; 16(11): 1786-94. PMID 16126738

47. Thewes B, Meiser B, Duric VM, et al. What survival benefits do premenopausal patients with early breast cancer need to make endocrine therapy worthwhile?. *Lancet Oncol.* Aug 2005; 6(8): 581-8. PMID 16054569
48. Henderson IC. *Breast cancer: fundamentals of evidence-based disease management.* New York: Oxford University Press; 2015.
49. Hamelinck VC, Bastiaannet E, Pieterse AH, et al. A Prospective Comparison of Younger and Older Patients' Preferences for Adjuvant Chemotherapy and Hormonal Therapy in Early Breast Cancer. *Clin Breast Cancer.* Oct 2016; 16(5): 379-388. PMID 27212474
50. Buus R, Sestak I, Kronenwett R, et al. Comparison of EndoPredict and EPclin With Oncotype DX Recurrence Score for Prediction of Risk of Distant Recurrence After Endocrine Therapy. *J Natl Cancer Inst.* Nov 2016; 108(11). PMID 27400969
51. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* Dec 30 2004; 351(27): 2817-26. PMID 15591335
52. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol.* Aug 10 2006; 24(23): 3726-34. PMID 16720680
53. Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. *Breast Cancer Res Treat.* May 2011; 127(1): 133-42. PMID 21221771
54. Sparano JA, Gray RJ, Makower DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med.* Nov 19 2015; 373(21): 2005-14. PMID 26412349
55. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med.* Jul 12 2018; 379(2): 111-121. PMID 29860917
56. Sestak I, Buus R, Cuzick J, et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncol.* Apr 01 2018; 4(4): 545-553. PMID 29450494
57. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res.* Sep 15 2011; 17(18): 6012-20. PMID 21807638
58. Sestak I, Martin M, Dubsky P, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. *Breast Cancer Res Treat.* Jul 2019; 176(2): 377-386. PMID 31041683
59. Sgroi DC, Sestak I, Cuzick J, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. *Lancet Oncol.* Oct 2013; 14(11): 1067-1076. PMID 24035531
60. Zhang Y, Schnabel CA, Schroeder BE, et al. Breast cancer index identifies early-stage estrogen receptor-positive breast cancer patients at risk for early- and late-distant recurrence. *Clin Cancer Res.* Aug 01 2013; 19(15): 4196-205. PMID 23757354
61. Bueno-de-Mesquita JM, Sonke GS, van de Vijver MJ, et al. Additional value and potential use of the 70-gene prognosis signature in node-negative breast cancer in daily clinical practice. *Ann Oncol.* Sep 2011; 22(9): 2021-2030. PMID 19955335
62. van 't Veer LJ, Yau C, Yu NY, et al. Tamoxifen therapy benefit for patients with 70-gene signature high and low risk. *Breast Cancer Res Treat.* Nov 2017; 166(2): 593-601. PMID 28776283
63. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. *N Engl J Med.* Aug 25 2016; 375(8): 717-29. PMID 27557300
64. Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol.* Aug 01 2013; 31(22): 2783-90. PMID 23816962
65. Grant M, Filipits M, Greil R, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. *Ann Oncol.* Feb 2014; 25(2): 339-45. PMID 24347518

66. Albain KS, Barlow WE, Shak S, et al. 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.* Jan 2010; 11(1): 55-65. PMID 20005174
67. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol.* Apr 10 2010; 28(11): 1829-34. PMID 20212256
68. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat.* Oct 2017; 165(3): 573-583. PMID 28664507
69. Nitz U, Gluz O, Clemens M, et al. West German Study PlanB Trial: Adjuvant Four Cycles of Epirubicin and Cyclophosphamide Plus Docetaxel Versus Six Cycles of Docetaxel and Cyclophosphamide in HER2-Negative Early Breast Cancer. *J Clin Oncol.* Apr 01 2019; 37(10): 799-808. PMID 30785826
70. Grant M, Sestak I, Filipits M, et al. Identifying clinically relevant prognostic subgroups of postmenopausal women with node-positive hormone receptor-positive early-stage breast cancer treated with endocrine therapy: a combined analysis of ABCSG-8 and ATAC using the PAM50 risk of recurrence score and intrinsic subtype. *Ann Oncol.* Aug 2015; 26(8): 1685-91. PMID 25935792
71. Filipits M, Dubsy P, Rudas M, et al. Prediction of Distant Recurrence Using EndoPredict Among Women with ER + , HER2 - Node-Positive and Node-Negative Breast Cancer Treated with Endocrine Therapy Only. *Clin Cancer Res.* Jul 01 2019; 25(13): 3865-3872. PMID 31064782
72. Jasem J, Fisher CM, Amini A, et al. The 21-Gene Recurrence Score Assay for Node-Positive, Early-Stage Breast Cancer and Impact of RxPONDER Trial on Chemotherapy Decision-Making: Have Clinicians Already Decided?. *J Natl Compr Canc Netw.* Apr 2017; 15(4): 494-503. PMID 28404760
73. Roberts MC, Miller DP, Shak S, et al. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. *Breast Cancer Res Treat.* Jun 2017; 163(2): 303-310. PMID 28243896
74. Harris LN, Ismaila N, McShane LM, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* Apr 01 2016; 34(10): 1134-50. PMID 26858339
75. Ettl J, Anders SI, Hapfelmeier A, et al. First prospective outcome data for the second-generation multigene test Endopredict in ER-positive/HER2-negative breast cancer. *Arch Gynecol Obstet.* Dec 2020; 302(6): 1461-1467. PMID 32902674
76. Mook S, Schmidt MK, Viale G, et al. The 70-gene prognosis-signature predicts disease outcome in breast cancer patients with 1-3 positive lymph nodes in an independent validation study. *Breast Cancer Res Treat.* Jul 2009; 116(2): 295-302. PMID 18661261
77. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst.* May 15 2013; 105(10): 701-10. PMID 23641039
78. Esserman L, Gallant E, Alvarado M. Less Is More: The Evolving Surgical Approach to Breast Cancer. *Am Soc Clin Oncol Educ Book.* 2016; 35: e5-e10. PMID 27249759
79. Dowsett M, Sestak I, Regan MM, et al. Integration of Clinical Variables for the Prediction of Late Distant Recurrence in Patients With Estrogen Receptor-Positive Breast Cancer Treated With 5 Years of Endocrine Therapy: CTS5. *J Clin Oncol.* Jul 01 2018; 36(19): 1941-1948. PMID 29676944
80. Dubsy P, Brase JC, Jakesz R, et al. The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. *Br J Cancer.* Dec 10 2013; 109(12): 2959-64. PMID 24157828
81. Filipits M, Nielsen TO, Rudas M, et al. The PAM50 risk-of-recurrence score predicts risk for late distant recurrence after endocrine therapy in postmenopausal women with endocrine-responsive early breast cancer. *Clin Cancer Res.* Mar 01 2014; 20(5): 1298-305. PMID 24520097
82. Sestak I, Cuzick J, Dowsett M, et al. Prediction of late distant recurrence after 5 years of endocrine treatment: a combined analysis of patients from the Austrian breast and colorectal cancer study group 8

- and arimidex, tamoxifen alone or in combination randomized trials using the PAM50 risk of recurrence score. *J Clin Oncol*. Mar 10 2015; 33(8): 916-22. PMID 25332252
83. Sestak I, Dowsett M, Zabaglo L, et al. Factors predicting late recurrence for estrogen receptor-positive breast cancer. *J Natl Cancer Inst*. Oct 02 2013; 105(19): 1504-11. PMID 24029245
 84. Esserman LJ, Yau C, Thompson CK, et al. Use of Molecular Tools to Identify Patients With Indolent Breast Cancers With Ultralow Risk Over 2 Decades. *JAMA Oncol*. Nov 01 2017; 3(11): 1503-1510. PMID 28662222
 85. Sgroi DC, Carney E, Zarrella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. *J Natl Cancer Inst*. Jul 17 2013; 105(14): 1036-42. PMID 23812955
 86. Schroeder B, Zhang Y, Stal O, et al. Risk stratification with Breast Cancer Index for late distant recurrence in patients with clinically low-risk (T1N0) estrogen receptor-positive breast cancer. *NPJ Breast Cancer*. 2017; 3: 28. PMID 28795152
 87. Delahaye LJM, Drukker CA, Dreezen C, et al. A breast cancer gene signature for indolent disease. *Breast Cancer Res Treat*. Jul 2017; 164(2): 461-466. PMID 28451965
 88. Burstein HJ, Griggs JJ, Prestrud AA, et al. American society of clinical oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Oncol Pract*. Sep 2010; 6(5): 243-6. PMID 21197188
 89. Lehmann BD, Jovanovic B, Chen X, et al. Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection. *PLoS One*. 2016; 11(6): e0157368. PMID 27310713
 90. Masuda H, Baggerly KA, Wang Y, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. *Clin Cancer Res*. Oct 01 2013; 19(19): 5533-40. PMID 23948975
 91. Bosl A, Spitzmuller A, Jasarevic Z, et al. MammaPrint versus EndoPredict: Poor correlation in disease recurrence risk classification of hormone receptor positive breast cancer. *PLoS One*. 2017; 12(8): e0183458. PMID 28850621
 92. Sestak I, Zhang Y, Schroeder BE, et al. Cross-Stratification and Differential Risk by Breast Cancer Index and Recurrence Score in Women with Hormone Receptor-Positive Lymph Node-Negative Early-Stage Breast Cancer. *Clin Cancer Res*. Oct 15 2016; 22(20): 5043-5048. PMID 27252417
 93. Hornberger J, Alvarado MD, Rebecca C, et al. Clinical validity/utility, change in practice patterns, and economic implications of risk stratifiers to predict outcomes for early-stage breast cancer: a systematic review. *J Natl Cancer Inst*. Jul 18 2012; 104(14): 1068-79. PMID 22767204
 94. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med*. Aug 10 2006; 355(6): 560-9. PMID 16899776
 95. Espinosa E, Vara JA, Redondo A, et al. Breast cancer prognosis determined by gene expression profiling: a quantitative reverse transcriptase polymerase chain reaction study. *J Clin Oncol*. Oct 10 2005; 23(29): 7278-85. PMID 16129846
 96. Kelly CM, Bernard PS, Krishnamurthy S, et al. Agreement in risk prediction between the 21-gene recurrence score assay (Oncotype DX(R)) and the PAM50 breast cancer intrinsic Classifier in early-stage estrogen receptor-positive breast cancer. *Oncologist*. 2012; 17(4): 492-8. PMID 22418568
 97. Prat A, Parker JS, Fan C, et al. Concordance among gene expression-based predictors for ER-positive breast cancer treated with adjuvant tamoxifen. *Ann Oncol*. Nov 2012; 23(11): 2866-2873. PMID 22532584
 98. Badve SS, Baehner FL, Gray RP, et al. Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory. *J Clin Oncol*. May 20 2008; 26(15): 2473-81. PMID 18487567
 99. Khoury T, Yan L, Liu S, et al. Oncotype DX RT-qPCR assay for ER and PR correlation with IHC: a study of 3 different clones. *Appl Immunohistochem Mol Morphol*. Mar 2015; 23(3): 178-87. PMID 24992175
 100. Drukker CA, Elias SG, Nijenhuis MV, et al. Gene expression profiling to predict the risk of locoregional recurrence in breast cancer: a pooled analysis. *Breast Cancer Res Treat*. Dec 2014; 148(3): 599-613. PMID 25414025

101. Fitzal F, Filipits M, Rudas M, et al. The genomic expression test EndoPredict is a prognostic tool for identifying risk of local recurrence in postmenopausal endocrine receptor-positive, her2neu-negative breast cancer patients randomised within the prospective ABCSG 8 trial. *Br J Cancer*. Apr 14 2015; 112(8): 1405-10. PMID 25867274
102. Krop I, Ismaila N, Stearns V. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Focused Update Guideline Summary. *J Oncol Pract*. Nov 2017; 13(11): 763-766. PMID 28696818
103. Andre F, Ismaila N, Henry NL, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: ASCO Clinical Practice Guideline Update-Integration of Results From TAILORx. *J Clin Oncol*. Aug 01 2019; 37(22): 1956-1964. PMID 31150316
104. Henry NL, Somerfield MR, Abramson VG, et al. Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer: Update of the ASCO Endorsement of the Cancer Care Ontario Guideline. *J Clin Oncol*. Aug 01 2019; 37(22): 1965-1977. PMID 31206315
105. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. *J Clin Oncol*. Feb 10 2019; 37(5): 423-438. PMID 30452337
106. Curigliano G, Burstein HJ, Winer EP, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol*. Aug 01 2017; 28(8): 1700-1712. PMID 28838210
107. Burstein HJ, Curigliano G, Loibl S, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol*. Oct 01 2019; 30(10): 1541-1557. PMID 31373601
108. Shah C, Bremer T, Cox C, et al. The Clinical Utility of DCISionRT (R) on Radiation Therapy Decision Making in Patients with Ductal Carcinoma In Situ Following Breast-Conserving Surgery. *Ann Surg Oncol*. Oct 2021; 28(11): 5974-5984. PMID 33821346

[CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS](#)

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.

