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

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OVERVIEW

Laboratory tests have been developed to detect the expression, via messenger RNA, of 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 the postsurgical management of breast cancer, to alter treatment in patients with ductal carcinoma in situ (DCIS), or to recommend extended endocrine therapy in patients who are recurrence-free at five years.

The following tests are addressed in this policy:

- Breast Cancer Index (Biotheranostics)
- Oncotype DX Breast (Genomic Health)
- Prosigna (NanoString Technologies)
- MammaPrint (Agendia)
- EndoPredict (Myriad)
- Oncotype DX Breast DCIS (Ductal Carcinoma In Situ) Score (Genomic Health)
- BluePrint (Agendia)

MEDICAL CRITERIA

BlueCHiP for Medicare

Breast Cancer Index – CPT 81518

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, M0); and
• Patient is lymph node negative
• 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

Oncotype DX Breast may be considered medically necessary for patients 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

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
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;
- who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors);
- 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 cm or 2.1 to 5 cm
- Grade: moderately differentiated; tumor size, any size
- Grade: poorly differentiated or undifferentiated; tumor size, any size

EndoPredict – 81522
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 – 0045U
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.

<u>Commercial Products</u>
Prior authorization is recommended for Commercial Products for the following tests and medical criteria can be found in the online authorization tool.

- Breast Cancer Index
- Oncotype DX Breast
- Prosigna
- MammaPrint

- EndoPredict

PRIOR AUTHORIZATION

BlueCHiP for Medicare

Prior authorization is required for BlueCHiP for Medicare for the following tests:

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

Commercial Products

Prior authorization is recommended for Commercial Products for the following tests and can be obtained via the online authorization tool for participating providers:

- Breast Cancer Index
- Oncotype DX Breast
- Prosigna
- MammaPrint
- EndoPredict

BlueCHiP for Medicare 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

BlueCHiP for Medicare

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

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

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

- BluePrint

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

- Breast Cancer Index
- Oncotype DX Breast
- Prosigna
- MammaPrint
- EndoPredict

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

- Oncotype DX Breast DCIS Score
- BluePrint

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 or EndoPredict) is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

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 patients 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, M0), node-negative, 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 patients:

- 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 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
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 a patients' risk for distant metastasis.

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 patients 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 patients.

Commercial Products
For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS Score, the evidence includes a prospective-retrospective study and a retrospective cohort study. Although the studies have shown that the test stratifies patients into high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in patients identified with a Breast DCIS Score is low enough to consider changing the management of DCIS. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

BlueCHiP for Medicare and Commercial Products
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.

CODING

The following CPT codes may be considered medically necessary for BlueCHiP for Medicare and Commercial Products when the medical criteria 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 (New Code Effective 1/1/2020)

The following CPT code is covered for BlueCHiP for Medicare when medical criteria above are met and is not medically necessary for Commercial Products:
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 codes requires prior authorization for BlueCHiP for Medicare 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

Genetic Testing Services
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, June 2020

REFERENCES

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Breast Cancer IndexTM (BCI) Gene Expression Test (L37822)
2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Breast Cancer IndexTM (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 Article: Billing and Coding: MolDX: MammaPrint (A54445)
8. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: ENDOPREDICT® Breast Cancer Gene Expression Test (L37311)
9. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: ENDOPREDICT® Breast Cancer Gene Expression Test (A57608)
10. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™) (L36941)
11. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Oncotype DX® Breast Cancer for DCIS (Genomic Health™) (A57619)
12. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: BLUEPRINT® Test (A55115)
13. 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):927-935. PMID 26786933.
14. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3.2019. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed September 30, 2019.
15. 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):3784-3796. PMID 20625130.
16. 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):2255-2269. PMID 24868023.
17. Burstein, HH, Lacchetti, CC, Anderson, HH, Buchholz, TT, Davidson, NN, Gelmon, KK, Giordano, SS, Hudis, CC, Solky, AA, Stearns, VV, Winer, EE, Griggs, JJ. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update. J. Clin. Oncol., 2018 Nov 20;37(5). PMID 30452337.
18. 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 1 2013;31(31):3997-4013. PMID 24101045.
19. Early Breast Cancer Trialists' Collaborative Group, Davies C, Godwin J, 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):771-784. PMID 21802721.

20. 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):1828-1833. PMID 8961972.
21. 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):684-690. PMID 11333290.
22. 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):456-462. PMID 11259471.
23. 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):805-816. PMID 23219286.
24. Gray RG, Rea D, Handley K, et al. aTTom: 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.
25. 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):1845-1853. PMID 18073378.
26. 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):1793-1802. PMID 14551341.
27. 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):1262-1271. PMID 16145047.
28. 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):1965-1971. PMID 18332472.