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

EFFECTIVE DATE: 04|01|2023
POLICY LAST UPDATED: 12|21|2022

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)
- Oncotype DX Breast (Genomic Health)
- Prosigna (NanoString Technologies)
- MammaPrint (Agendia)
- EndoPredict (Myriad)
- MammaPrint NGS (Agendia)
- Oncotype DX Breast DCIS (Ductal Carcinoma In Situ) Score (Genomic Health)
- BluePrint (Agendia)
- Insight TNBCtype (Insight Molecular Labs)
- DCISionRT® (Prelude Corporation)

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 (Effective 1/1/2022)
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.
Please refer to the Policy Statement for 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.

Insight TNBCtype – CPT 0153U
Insight TNBCtype may be considered medically necessary when the Medicare Advantage Plans medical necessity criteria is used for review, found in the Medical Necessity policy. Please see Related Policies section. Please refer to the Policy Statement for Commercial Products.

PRIOR AUTHORIZATION

Medicare Advantage Plans
Prior authorization is required for Medicare Advantage Plans for the following tests:

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

Commercial Products
Prior authorization is recommended for Commercial Products for the following tests:

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

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 considered medically necessary when the medical criteria in the Medical Necessity policy are met:

- Insight TNBCtype

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
- 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
- Insight TNBCtype
- Oncotype DX Breast DCIS Score

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.

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.

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 individuals into high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in individuals 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.

Medicare Advantage Plans 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.

Insight TNBCtype
The Insight TNBCtype uses next-generation sequencing to classify expression data from 101 genes into 5 molecular subtypes including basal-like 1 (BL1), basal-like 2 (BL2), luminal androgen receptor (LAR), mesenchymal stem-like (MSL), and mesenchymal (M), as well as a complementary immunomodulatory (IM) classifier. The stated purpose of the test is to help direct selection and combination of chemotherapies and to support development of novel TNBC targeted therapeutics and diagnostics.

Medicare Advantage Plans and Commercial Products
For individuals who have TNBC considering neoadjuvant chemotherapy who receive gene expression profiling with the Insight TNBCtype test, the evidence includes retrospective cohort studies. Although the studies have shown that TNBC subtypes may differ in their response to neoadjuvant chemotherapy, as the studies were not prospectively designed or powered to specifically address the TNBC population or their specific therapeutic questions, conclusions cannot be drawn based on these findings. Additional Simon et al (2009) category A or B studies are required. Additionally, further clarity about how the test would inform clinical practice is still needed. 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 hanging 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 (Code Effective 1/1/2022)

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

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 covered for Medicare Advantage Plans when medical criteria found in the Medical Necessity policy are met and are not medically necessary for Commercial Products.

This code can be used for Insight TNBCtype:

0153U Oncology (breast), mRNA, gene expression profiling by next-generation sequencing of 101 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a triple negative breast cancer clinical subtype(s) with information on immune cell involvement

The following CPT code is not covered for Medicare Advantage Plans and is 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

Genetic Testing Services
Medical Necessity
Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, February 2023
Provider Update, February 2022
Provider Update, September 2021
Provider Update, June 2021
Provider Update, June 2020

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