Breast Cancer Index for Breast Cancer Prognosis

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Breast Cancer Index (BCI) for breast cancer prognosis is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
Breast Cancer Index	81518

Criteria

Requests for Breast Cancer Index (BCI) testing are reviewed using the following criteria.

Criteria

- For prognostic testing for adjuvant chemotherapy decision making
  - No previous gene expression assay on the same tumor when a prognostic result was previously successfully obtained, AND
  - Required Clinical Characteristics at Initial Diagnosis:
    - Primary invasive breast cancer meeting all of the following criteria:
    - Unilateral tumor
      - Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3), and
      - Hormone receptor positive (ER+ or PR+), and
      - Human epidermal growth factor receptor 2 (HER2) negative, AND
  - Individual has no regional lymph node metastasis (pN0) or only micrometastases (pN1mi, malignant cells in regional lymph node(s) not greater than 2.0 mm), and
  - Adjuvant endocrine systemic chemotherapy is a planned treatment option for the individual or results from this Breast Cancer Index test will be used in making adjuvant chemotherapy treatment decision, AND
  - Rendering laboratory is a qualified provider of service per the Health Plan policy.
- For predictive testing for extended endocrine therapy decision making

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- No previous gene expression assay on the same tumor when a predictive result was previously successfully obtained, AND
- Required Clinical Characteristics at Initial Diagnosis:
  - Primary invasive breast cancer meeting all of the following criteria:
  - Unilateral tumor:
    - Hormone receptor positive (ER+ or PR+), and
    - Human epidermal growth factor receptor 2 (HER2) negative, AND
- Individual has involvement of 0-3 ipsilateral axillary lymph nodes, and
- Extended endocrine therapy beyond five years is a treatment option for the individual and results from this Breast Cancer Index test will be used in making extended endocrine therapy treatment decisions, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

Testing Multiple Samples:

- When more than one ipsilateral breast cancer primary is diagnosed, testing should be performed on the tumor with the most aggressive histologic characteristics. If an exception is requested, the following criteria will apply:
  - There should be reasonable evidence that the tumors are distinct (e.g., different quadrants, different histopathologic features, etc.), AND
  - There should be no evidence from either tumor that chemotherapy is indicated (e.g., histopathologic features or previous Breast Cancer Index result of one tumor suggest chemotherapy is indicated), AND
  - If both tumors are to be tested, both tumors must independently meet the required clinical characteristics.

What is Breast Cancer Index for breast cancer prognosis?

Breast Cancer Index® (BCI) is a commercial multigene expression profiling assay designed to assess prognosis in individuals with early-stage breast cancer.[1]

Breast Cancer Recurrence

A large percentage of individuals with breast cancer (ER+ [estrogen receptor positive]/ LN- [lymph node-negative]) treated with endocrine therapy alone are free of disease 10+ years after initial diagnosis, and could forgo chemotherapy and its toxic side effects. Furthermore, a meta-analysis (n=~35,000 individuals) reported a rate of recurrence of ~2% per year for individuals with breast cancer (ER+/LN-) receiving only tamoxifen.[2] Consequently, accurate prediction of the risk of breast cancer recurrence is important

for establishing the most optimal course of treatment with endocrine therapy, adjuvant chemotherapy, or both for individuals with early-stage breast cancer.

Risk Assessment

Conventional methods of risk assessment include using the following clinicopathologic factors

- tumor size
- involvement of regional lymph nodes
- histologic grade
- expression of hormone receptors (estrogen and progesterone), and
- human epidermal growth factor receptor 2 (HER2) amplification.

These may not be sufficiently accurate to identify those subgroups of individuals who are at low risk of recurrence and who are unlikely to benefit from extended endocrine therapy or adjuvant chemotherapy.[3]

As a result, alternative biomarker prognostic tests have been developed to more accurately predict individual risk of cancer recurrence and to better inform clinicians making treatment decisions for individuals with early-stage breast cancer, including

- determining appropriate chemotherapy regimens
- decreasing treatment-associated complications, and
- avoiding unnecessary treatment.[4]

Intended Use

According to the manufacturer, "The Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test is indicated for use in women diagnosed with hormone receptor-positive (HR+), lymph node-negative (LN-) or lymph node-positive (LN+; with 1-3 positive nodes) early-stage, invasive breast cancer, who are distant recurrence-free. The BCI test provides: 1) a quantitative estimate of the risk for both late (post-5 years from diagnosis) distant recurrence and of the cumulative distant recurrence risk over 10 years (0-10y) in patients treated with adjuvant endocrine therapy (LN- patients) or adjuvant chemoendocrine therapy (LN+ patients), and 2) prediction of the likelihood of benefit from extended (>5 year) endocrine therapy. BCI results are adjunctive to the ordering physician's workup; treatment decisions require correlation with all other clinical findings."[1]

Test information

The test is intended to provide risk information beyond standard predictive and prognostic factors and identify those individuals unlikely to benefit from extended endocrine therapy or adjuvant chemotherapy.[1]

Breast Cancer Index

The BCI assay is an algorithmic gene expression-based signature, which combines 2 independent biomarkers (HOXB13:IL17BR [H:I or H/I] and the 5-gene molecular grade index (MGI) to evaluate estrogen-mediated signaling and tumor grade.[2]

As a risk stratification tool, BCI attempts to stratify individuals with early-stage ER+/LN- into three different risk groups, as well offer a continuous evaluation of an individual's risk of distant recurrence.[2]

Guidelines and evidence

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO, 2022) published a clinical practice guideline regarding the use of biomarkers to guide clinical decision-making on adjuvant systemic therapy among individuals with early-stage invasive breast cancer. Based on a review of the peer-reviewed scientific evidence, the following recommendations were published:[5]

- "If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)."
- "If a patient has node-positive breast cancer with 4 or more positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong)."
- "If a patient has HER2-positive breast cancer or TNBC [triple negative breast cancer], the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong)."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) Clinical Practice Guidelines for Breast Cancer provided evaluations of various multigene assays used to determine whether adjuvant systemic chemotherapy should be added to adjuvant

endocrine therapy.[6] With regard to prognostic use of the BCI assay, the NCCN stated the following (with evidence level of category 2A):[6]

- BCI is listed as predictive of benefit of extended adjuvant endocrine therapy and as prognostic.
- "For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) in the low-risk range (0-5), regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. Patients with BCI (H/I) low demonstrated a lower risk of distant recurrence (compared to BCI [H/I] high) and no significant improvement in disease free survival (DFS) or OS [overall survival] compared to control arm in terms of extending endocrine therapy duration."
- "For patients with T1 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) high (5.1-10) demonstrated significant rates of late distant recurrence. In secondary analyses of the MA.17, Trans-aTTom, and IDEAL trials, patients with HR-positive, T1-T3, pN0 or pN+ who had a BCI (H/I) high demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared to the control arm."
- "The benefit of testing BCI (H/I) for extended adjuvant endocrine therapy is unknown in patients who had ovarian function suppression, CDK4/6 inhibitors, or olaparib in addition to adjuvant endocrine therapy."

Ontario Health (Cancer Care Ontario) Program in Evidence-Based Care

The Ontario Health (Cancer Care Ontario) Program in Evidence-Based Care (PEBC, 2022) conducted a systematic review of the literature to serve as the basis of their clinical practice guideline. The clinical practice guideline for the clinical utility of multigene profiling assays in early-stage invasive breast cancer stated the following regarding BCI:[7]

- For early stage ER-positive and HER2-negative breast cancer, consider using multigene profiling assays, such as BCI, to assist with guiding the decision regarding systemic therapy.
- For early stage node-negative, ER-positive, HER2-negative breast cancer, a low-risk result from multigene profiling assays, such as BCI, may support a decision to not use adjuvant chemotherapy.
- "The evidence to support the use of molecular profiling to select the duration of endocrine therapy is evolving. In patients with ER-positive disease, clinicians may consider using a Breast Cancer Index (H/I) high assay result to support a decision to extend adjuvant endocrine therapy if the decision is supported by other clinical, pathological, or patient-related factors."

St. Gallen International Expert Consensus

The St. Gallen International Expert Consensus (2017) stated the following:

- "The Panel did not recommend the use of gene expression signatures for choosing whether to recommend extended adjuvant endocrine treatment, as no prospective data exist and the retrospective data were not considered sufficient to justify the routine use of genomic assays in this setting."[8]

Selected Relevant Publications

Several retrospective and prospective-retrospective studies, published by the manufacturer, have assessed the clinical validity of the BCI test for individuals with early stage breast cancer (ER+/LN-) to guide clinical decision making regarding adjuvant therapy (prognostic) or regarding treatment response (predictive).[2,9-17] Results of clinical validity are generally consistent across these studies, reporting that individuals classified by the BCI test into higher risk categories tend to have worse rates of distant recurrence, and individuals in lower risk categories have better rates of distant recurrence.

There is evidence that the BCI test is predictive of extended endocrine therapy benefit. Two retrospective studies evaluating subsets of individuals from the IDEAL and ATAC trials found that BCI was significantly associated with extended letrozole benefit.[10,15] Two retrospective analyses of individuals from the Trans-aTTom trial, both by the same author, assessed BCI for predicting extended tamoxifen benefit.[14,17] The first study of a small subset of individuals who were node-positive and postmenopausal found that the test was associated with individuals who experienced a benefit from extended therapy. The second study included individuals with varying nodal (32% node-positive) and menopausal statuses (86% postmenopausal). Notably, the overall and node-negative cohorts were underpowered due to low even rates. In the node-positive group, BCI results were significantly associated with a benefit from extended therapy. Several individual study limitations were identified across the evidence for the predictive use of the test including: limited numbers of premenopausal individuals, wide confidence intervals, potential selection bias, and retrospective study designs. A systematic review evaluated the clinical validity and clinical utility of five breast cancer GEP assays, including BCI. Study authors indicated that BCI may identify individuals likely to benefit from extended endocrine therapy. This review was hampered by several limitations, including a non-comprehensive literature search and an insufficient assessment of individual study bias and heterogeneity.[18]

The evidence for the use of BCI as a prognostic test in node-positive individuals is sparse and of low quality. Additional well-designed clinical trials are needed that evaluate the prognostic performance of BCI in large populations of node positive individuals currently receiving endocrine therapy and adjuvant chemotherapy.[19,20]

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Breast Cancer Index will ensure that testing will be

available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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