Introduction

Breast Cancer Index 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.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
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What is Breast Cancer Index for breast cancer prognosis

Definition

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

Breast cancer recurrence

A large percentage of breast cancer patients (ER+/LN-) 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 patients) reported a rate of recurrence of ~2% per year for breast cancer patients (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 women with early-stage breast cancer.

Risk assessment

Conventional methods of risk assessment including using the following clinicopathologic factors

- tumor size
- involvement of regional lymph nodes
- histologic grade

1. [Reference 1]
2. [Reference 2]
• 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 patients who are at low risk of recurrence and who are unlikely to benefit from extended endocrine therapy or adjuvant chemotherapy.\textsuperscript{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 patients with early-stage breast cancer, including

• determining appropriate chemotherapy regimens
• decreasing treatment-associated complications, and
• avoiding unnecessary treatment.\textsuperscript{4}

**Intended use**

According to the manufacturer, "The Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test is intended for use in patients diagnosed with estrogen receptor-positive (ER+), lymph node-negative (LN-) or lymph node positive (LN+; with 1-3 positive nodes) early-stage, invasive breast cancer, who are distant recurrence-free. BCI provides:

• A quantitative assessment of the likelihood of both late (post-5 years) and overall (0-10 year) distant recurrence following an initial 5 years of endocrine therapy (LN- patients) or 5 years of endocrine therapy plus adjuvant chemotherapy (LN+ patients), and
• Prediction of 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."\textsuperscript{1}

**Test information**

**Introduction**

The test is intended to provide risk information beyond standard predictive and prognostic factors and identify those patients unlikely to benefit from extended endocrine therapy or adjuvant chemotherapy.\textsuperscript{1}

**Breast Cancer Index**

The Breast Cancer Index 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.\textsuperscript{2}
As a risk stratification tool, BCI attempts to stratify patients with early-stage estrogen-receptor positive (ER+), lymph-node negative (LN-) patients into three different risk groups, as well offer a continuous evaluation of an individual patient’s risk of distant recurrence.²

**Guidelines and evidence**

**Introduction**

This section includes relevant guidelines and evidence pertaining to Breast Cancer Index testing.

**The National Comprehensive Cancer Network**

The National Comprehensive Cancer Network (NCCN) 2019 Clinical Practice Guidelines for Breast Cancer provide evaluations of various multigene assays used to evaluate whether adjuvant systemic chemotherapy should be added to adjuvant endocrine therapy.² With regard to prognostic use of the Breast Cancer Index (BCI) assay, the NCCN states the following (with evidence level of category 2A):⁵

- “For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. There are limited data as to the role of BCI in hormone receptor-positive, HER2-negative, and lymph node-positive breast cancer.”
- Use of the test for predictive purposes has not been determined.

**St. Gallen International Expert Consensus**

St. Gallen International Expert Consensus (updated 2017)

- “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.”⁶

**American Society of Clinical Oncology**

The American Society of Clinical Oncology (ASCO, 2016) published a clinical practice guideline regarding the use of biomarkers to guide clinical decision-making on adjuvant systemic therapy among women with early-stage invasive breast cancer. Based on a review of the peer-reviewed scientific evidence, the following recommendations were published:⁷

- “If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the Breast Cancer Index to guide decisions on adjuvant

- "If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong."

- "If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the Breast Cancer Index to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong."

Peer Reviewed Literature

Several retrospective and prospective-retrospective studies, published by the manufacturer, have assessed the clinical validity of the BCI test for women with early stage breast cancer (ER+/LN-) to guide clinical decision making regarding adjuvant therapy (prognostic) or regarding treatment response (predictive).\textsuperscript{2,8-13} Results of clinical validity are generally consistent across these studies, reporting that women classified by the BCI test into higher risk categories tend to have worse rates of distant recurrence, and women in lower risk categories have better rates of distant recurrence.

Criteria

Introduction

Requests for Breast Cancer Index testing are reviewed using these criteria.

Criteria

- Previous Testing:
  - No repeat Breast Cancer Index testing on the same tumor when a result was successfully obtained, and
  - No previous gene expression assay (e.g. OncotypeDx Breast) performed on the same tumor when a result was successfully obtained, AND

- Required Clinical Characteristics:
  - 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
      - HER2 negative, and
- Patient has no regional lymph node metastasis (pN0) or only micrometastases (pN1mi, malignant cells in regional lymph node(s) not greater than 2.0mm), and
- Adjuvant endocrine systemic chemotherapy is a planned treatment option for the patient or results from this Breast Cancer Index test will be used in making adjuvant chemotherapy 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

**References**

**Introduction**

These references are cited in this guideline.

1. Biotheranostics. The Breast Cancer Index (BCI). Available at: https://www.breastcancerindex.com/


