Clinical Policy Title: Breast cancer index genetic testing

Clinical Policy Number: 02.01.22

Effective Date: January 1, 2017
Initial Review Date: October 19, 2016
Most Recent Review Date: October 19, 2016
Next Review Date: October 2017

Policy contains:
- Breast Cancer Index

Related policies:
CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 13.01.01 Genetic testing for prostate cancer prognosis

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice considers the once-per-lifetime use of Breast Cancer Index® (BCI) genetic testing to be clinically proven and, therefore, medically necessary when the following criteria are met:
- Post-menopausal female with non-relapsed, hormone-receptor-positive breast cancer, and
- Is lymph node negative, and
- Is completing five years of tamoxifen therapy, and
- Patient must be eligible for consideration of extended endocrine therapy based on published clinical trial data or practice guidelines, and
- Physician or patient is concerned about continuing anti-hormonal therapy because of documented meaningful toxicity or possible significant patient-specific side effects.
- The test results will be discussed with the patient (including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test, and current cancer management guidelines), and
There is a care-coordinating, multidisciplinary team available for genetic and behavioral counseling for a tiered evaluation, which includes (a.) a primary care provider, (b.) a geneticist (who is a physician or a licensed genetic counselor), and

Patient desire for engagement with the integrated multidisciplinary team is documented in the clinical record.

**Limitations:**

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

Prestige Health Choice considers the routine use of BCI in the initial treatment planning and management of women with newly-diagnosed breast cancer to be investigational and, therefore, not medically necessary.

All other uses of BCI are considered investigational and, therefore, not medically necessary.

**Alternative covered services:**

Primary care and specialty physician (including surgical) evaluation and management.

**Background**

The BCI test from bioTheranostics analyzes the activity of seven genes to help predict the recurrence risk of early-stage, node-negative, hormone-receptor-positive breast cancer. It is helpful in making the decision to extend hormonal therapy beyond an initial 5-year course of therapy in women with hormone-receptor-positive breast cancer. The current National Comprehensive Cancer Network (NCCN 2015) guidelines recommend adjuvant treatment of women with hormone-receptor–positive tumors who are premenopausal at diagnosis (i.e., tamoxifen 5 to 10 years without ovarian suppression, and 5 years with ovarian suppression, or an aromatase inhibitor for 5 years combined with ovarian suppression or ablation).

The BCI assay may identify a subset of postmenopausal women who are at increased risk of late relapses for hormone-receptor-positive breast cancer and who may derive a greater benefit from extended hormone therapy. Current NCCN guidelines recommend adjuvant hormone therapy for postmenopausal patients with hormone-receptor-positive disease for 10 years (5 years initially and then strong consideration for an additional 5 years).

There is insufficient medical evidence to draw any conclusions about the use of BCI in the initial treatment planning and management of women with newly-diagnosed breast cancer.
Searches

Prestige Health Choice searched PubMed and the databases of:
- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on September 1, 2016. Searched terms were: "breast cancer (MeSH)", "BCI (MeSH)" and "breast cancer index."

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

Sgroi (2016) evaluated the prognostic value of BCI to determine whether biomarkers can be used to accurately assess risk of recurrence in 299 women with hormone-receptor–positive breast cancer. BCI had a significant prognostic effect [hazard ratio (HR) 2.34, 95 percent confidence interval (CI) 1.33–4.11; p = 0.004], although not a predictive effect, on relapse-free survival in stratified multivariate analysis, adjusted for pathological tumor stage (HR 2.22, 95 percent CI 1.22–4.07; p = 0.01). In a post hoc multivariate analysis, higher linear BCI was associated with shorter recurrence-free survival (p = 0.002). Moreover, BCI was prognostic in both lymph node-negative and node-positive disease.

Sanft (2015) studied physician recommendations for extended endocrine therapy after BCI testing. BCI predicted a low risk of late recurrence in 59 percent of patients versus intermediate/high recurrence risk in 24 percent and 17 percent, respectively. Physician recommendations for extended endocrine therapy changed for 26 percent of patients after considering BCI results, with a net decrease in recommendations for extended endocrine therapy from 74 percent to 54 percent. After BCI testing, fewer patients wanted to continue extended therapy and decision conflict (p = 0.031) and anxiety (p < 0.001) also decreased. The authors concluded that incorporation of BCI into risk/benefit discussions regarding extended endocrine therapy resulted in changes in treatment recommendations and improved patient satisfaction.
Sgroi (2013) evaluated the prognostic ability of the BCI in 1102 primary tumor samples from hormone-receptor-positive patients. Prognostic discrimination for early and late recurrence was assessed. BCI demonstrated significant differences in recurrence risk over 10 years (p <0·0001). For risk of early recurrence at ≤ 5 years, BCI classified 59 percent (390/665), 25 percent (166/665) and 16 percent (109/665) of patients with 1.3 percent (0.5 percent – 3.1 percent), 5.6 percent (2.9 percent – 10.5 percent) and 18.1 percent (12.0 percent – 27.0 percent) for low, intermediate and high risk, respectively. For risk of late recurrence at 10 years, BCI classified 61 percent (366/596), 25 percent (146/596) and 14 percent (84/596) of patients with 3.5 percent (2.0 percent – 6.1 percent), 13.4 percent (8.5 percent – 20.8 percent) and 13.3 percent (7.4 percent – 23.4 percent) for low, intermediate and high, respectively. Overall BCI identified groups at risk for both early and late recurrence with 84 percent (556/665) of patients having low risk, and a smaller population (39 percent, 230/596) having high risk for late recurrence who may benefit from extended endocrine or other therapy.

Jankowicz (2011) described the utility of BCI as a significant predictor of outcome in a cohort of 265 hormone-positive, lymph-node-negative breast cancer patients. BCI categorized 55 percent, 21 percent, and 24 percent of patients as low, intermediate and high-risk, respectively, for recurrence of disease. The 10-year rates of distant recurrence were 6.6 percent, 12.1 percent and 31.9 percent and of breast cancer-specific mortality were 3.5 percent, 3.6 percent and 22.1 percent in low, intermediate, and high-risk groups. In a multivariate analysis including clinico-pathological factors (e.g., age, stage) BCI was a significant predictor of distant recurrence (p = 0.0002) and breast cancer-specific mortality (p < 0.0001). The authors concluded that BCI testing in hormone-positive, lymph-node-negative patients was accurate in classification of recurrence risk at 10-years, risk of distant recurrence and breast cancer-specific death, and that BCI has additive utility beyond usual standard of care parameters.

Jerevall (2011) examined in a blinded retrospective analysis of 588 hormone-receptor-positive tamoxifen-treated and untreated breast cancer patients the ability of BCI to assess risk of recurrence in early-stage breast cancer patients. BCI identified a cohort of patients significantly associated with distant recurrence and breast cancer death. Tamoxifen-treated patients categorized as low-risk were found to have <3 percent 10-year distant recurrence risk while untreated patients categorized as low risk were associated with an 8.3 percent 10-year distant recurrence risk.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Sgroi (2016)</td>
<td><strong>Key points:</strong></td>
</tr>
</tbody>
</table>
| Assessment of the prognostic and predictive utility of the Breast Cancer Index (BCI): an NCIC CTG MA.14 study | - Evaluated the prognostic value of BCI to determine whether biomarkers can be used to accurately assess risk of recurrence in 299 women with hormone-receptor-positive breast cancer.  
- BCI had a significant prognostic effect [hazard ratio (HR) 2.34, 95 percent confidence interval (CI) 1.33–4.11; p = 0.004], although not a predictive effect, on relapse-free survival in stratified multivariate analysis, adjusted for pathological tumor stage (HR 2.22, 95 percent CI 1.22–4.07; p = 0.01). |
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| Sanft (2015) | - Studied physician recommendations for extended endocrine therapy after BCI testing.  
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  - After BCI testing, fewer patients wanted to continue extended therapy and decision conflict (p = 0.031) and anxiety (p < 0.001) also decreased.  
  - The authors concluded that incorporation of BCI into risk/benefit discussions regarding extended endocrine therapy resulted in changes in treatment recommendations and improved patient satisfaction. |
| Sgroi (2013) | - Evaluated the prognostic ability of the BCI in 1102 primary tumor samples from hormone-receptor-positive patients.  
  - BCI demonstrated significant differences in recurrence risk over 10 years (p <0·0001).  
  - Overall BCI identified groups at risk for both early and late recurrence with 84 percent (556/665) of patients having low risk, and a smaller population (39 percent, 230/596) having high risk for late recurrence who may benefit from extended endocrine or other therapy. |
| Jankowicz (2011) | - Described the utility of BCI as a significant predictor of outcome in a cohort of 265 hormone-positive, lymph-node-negative patients.  
  - BCI categorized 55 percent, 21 percent, and 24 percent of patients as low, intermediate and high-risk, respectively, for recurrence of disease.  
  - The 10-year rates of distant recurrence were 6.6 percent, 12.1 percent and 31.9 percent and of breast cancer-specific mortality were 3.8 percent, 3.6 percent and 22.1 percent in low, intermediate, and high-risk groups.  
  - In a multivariate analysis including clinico-pathological factors (e.g., age, stage) BCI was a significant predictor of distant recurrence (p = 0.0002)) and breast cancer-specific mortality (p < 0.0001)).  
  - BCI testing in hormone-positive, lymph-node-negative patients was accurate in classification of recurrence risk at 10-years, risk of distant recurrence and breast cancer-specific death, and that BCI has additive utility beyond usual standard of care parameters. |
Jerevall (2011)  
BCI Development and validation: Stockholm prospective study

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<tr>
<td>• Assessed the ability of BCI to assess risk of recurrence in early-stage breast cancer patients.</td>
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<td>• BCI identified a cohort of patients significantly associated with distant recurrence and breast cancer death.</td>
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<td>• Tamoxifen-treated patients categorized as low-risk were found to have &lt;3 percent 10-year distant recurrence risk while untreated patients categorized as low risk were associated with an 8.3 percent 10-year distant recurrence risk.</td>
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Glossary

**Early stage breast cancer** — Breast cancer which has not spread to distant parts of the body. Some experts consider spread to nearby lymph nodes (stage III) to be “early stage” in nature and will lump these cancers in with stage I and stage II breast cancer tumors.

**Hormone-positive** — A cancer is called hormone-receptor-positive if its cells have on their surface receptors for hormones (e.g., estrogen, progesterone). This suggests that the cancer cells may receive signals from hormones that could promote their growth, and conversely that withdrawal of hormones may retard the tumor’s growth.

**Hormonal therapy** — Hormone therapies used in breast cancer treatment block hormone actions or lower hormone levels in the body.

**Prognostic indicator** — Factors, such as staging, tumor type, and laboratory studies, that may indicate treatment effectiveness and outcomes.

References

Professional society guidelines/other:


Peer-reviewed references:


Clinical Trials:

Searched clinicaltrials.gov on September 1, 2016 using terms “breast cancer index” | Open Studies. 52 studies found, 1 relevant.

**CMS National Coverage Determination (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**


**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

<table>
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<tr>
<th>CPT Code</th>
<th>Description</th>
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<td>81519</td>
<td>Oncology(breast), mRNA, gene expression profiling by real time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a recurrence score</td>
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