Submitted by:
Catherine Schnabel, PhD
Chief Scientific Officer
bioTheranostics, Inc.
9620 Towne Centre Drive, Suite 200, San Diego, CA 92121
858-587-5884; cathy.schnabel@biotheranostics.com
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NCCN Guidelines Panel: Breast Cancer

On behalf of bioTheranostics Inc., I respectfully request the NCCN Panel to review the enclosed data in support of the Breast Cancer Index (BCI) for the molecular assessment of recurrence risk and to predict the likelihood of benefit from extended endocrine therapy in patients with node-negative, hormone receptor-positive (HR+) breast cancer who are completing adjuvant endocrine treatment. This information is highlighted below.

Specific Change: Recommend inclusion of the bioTheranostics' BCI assay as a component of the treatment guideline for node-negative, HER2-negative, HR+ tumors as a footnote in BINV-6 (Systemic Adjuvant Treatment) and/or BINV-16 (Surveillance/Follow-up).

As such, the requested change for consideration is as follows: For duration of endocrine therapy (5 vs 10 years), as appropriate based on menopausal status and endocrine treatment history (BINV-J), consider use of tumor-based molecular assay (Breast Cancer Index) to stratify based on likelihood of benefit from endocrine therapy and risk of late (>5y) recurrence.

Regulatory Status: BCI testing is conducted and results are generated at the bioTheranostics clinical laboratory in San Diego, CA; the laboratory is compliant and certified by the Clinical Laboratory Improvement Amendments (CLIA), accredited by the College of American Pathologists (CAP), and licensed in all 50 states.

Rigorous review through the CMS MolDx program has determined that BCI meets the clinical validity and clinical utility standards and is covered as a reasonable and necessary Medicare benefit.

Rationale: While it is well established that many women with hormone receptor-positive tumors can benefit from longer duration of adjuvant endocrine therapy beyond five years, it is also recognized that only a subset of these women truly benefit from prolonged therapy.[1-5] The cost, inconvenience, and toxicities of endocrine therapy can be significant for many women, making it important to be able to use a validated approach for appropriate patient selection. This issue is clinically-significant given that the number-needed-to-treat is high and the risk-benefit assessment is significant in the extended endocrine setting.[1-5] The BCI assay, which has been studied in over 8,000 patients, provides individualized risk assessment and predictive data, which can lead to a less variable approach in the identification of patients who may be adequately treated with 5 years of adjuvant endocrine therapy vs those for whom 10 years of endocrine therapy should be recommended. BCI is the only available biomarker that is predictive for benefit from endocrine therapy.[6,8,13,14] Based on studies from clinical trial cohorts and clinical experience to date, approximately 40% of early stage patients are stratified by BCI as being likely to benefit from extended endocrine therapy.[6-9,12]

Methodology: BCI is a gene expression-based assay (RT-PCR of 11 genes) performed on RNA isolated from formalin-fixed paraffin-embedded primary tumor tissue that reports both a predictive and prognostic component:

- **Predictive:** A categorical result (high vs low) based on the HoxB13/IL17BR (H/I) endocrine response biomarker, where a high H/I ratio is predictive for likelihood of benefit from extended endocrine therapy.
- **Prognostic:** A continuous BCI Score provides an individualized risk of distant recurrence, including a distinct prediction for late recurrence (years 5-10). The BCI Score is derived from an algorithm that incorporates H/I with a set of proliferation-based genes.

Clinical Performance: BCI's prognostic and predictive components have been validated per the guidance issued in the 2011 NCCN Task Force Report, including validation in multiple prospective-retrospective studies using RCT cohorts (Level 1B evidence).[6-9] A summary table of supportive studies is provided below.

New BCI Data:

1) Investigators from an NCCN center (Yale Smilow Cancer Center) completed a clinical utility study demonstrating that clinical treatment decisions for extended endocrine therapy were changed based on BCI results in 27% of patients tested.[11]
2) In post-hoc studies from two randomized controlled trial cohorts (presented at SABCS 2014 and ASCO 2015) BCI Predictive (H/I) was found to be the only significant independent predictor of benefit from endocrine therapy compared to quantitative ER and PR.[13,14]

In closing, we gratefully acknowledge our investigators from several NCCN centers, and highlight for the committee that BCI is currently being clinically (e.g., outside of the investigational setting) in a number of major academic centers across the country.

We appreciate the opportunity to provide this information for consideration by the NCCN Breast Cancer Guideline Panel. If you have any questions or require additional information, please do not hesitate to contact me directly.

Sincerely,

Catherine Schnabel, PhD
Chief Scientific Officer
bioTheranostics, Inc

Key Clinical Study Overview

	Study Description	Clinical Trial	Reference
Predictive	Prediction of benefit of extended endocrine therapy (letrozole vs placebo)	MA.17	8
	Prediction of benefit of adjuvant endocrine therapy (tamoxifen vs untreated)	Stockholm	6
	Prediction of differential benefit of endocrine therapy (anastrozole vs tamoxifen)	TransATAC	7
Prognostic	Prognostication of risk of late distant recurrence in patients treated with adjuvant tamoxifen	Stockholm	6
	Prognostication of risk of late distant recurrence in patients treated with adjuvant tamoxifen or AI, and head-to-head study with 21-gene assay and IHC4 assay	TransATAC	9
	Prognostication of risk of late distant recurrence in patients treated with adjuvant tamoxifen	Multi-institutional	6

References

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