Catherine Schnabel, PhD
Vice President, Translational Science
bioTheranostics, Inc
9640 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

To the NCCN panel members:

On behalf of bioTheranostics Inc., I respectfully request the NCCN Breast Cancer Panel to review the enclosed published data for inclusion of the Breast Cancer Index (BCI) test in the NCCN Guideline clinical algorithm of extended endocrine therapy for hormone receptor-positive (HR+), early stage breast cancer. This information is highlighted below.

Specific Changes: Request addition of BCI into the NCCN Guideline (BINV-J) for patients with node-negative, HR+ tumors ≥ 0.5cm, as a complementary gene-based approach to other elements of risk stratification, and to aid in decision-making for extended endocrine therapy following completion of 5 years of adjuvant endocrine treatment. BCI estimates both the likelihood of late (>5 year) recurrence, and the benefit from extended endocrine therapy.[1-4]

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

Rationale: Several landmark clinical trials have demonstrated reduced risk of late relapse with extended endocrine therapy; however, only a limited subset of patients benefit (3-6% absolute benefit).[5-10] Furthermore, these and other endocrine therapy trials have shown clinically-significant toxicities and adverse events, including increased risk of endometrial cancer, pulmonary embolism, ischemic events, and loss of bone mineral density.[5-10] Accordingly, the decision to extend endocrine therapy requires a personalized approach to address risk vs benefit; however, clinicopathologic variables and other molecular tests do not provide individualized risk stratification and predictive information for late disease management.

Published, pivotal clinical studies[1-4] conducted by major academic centers that included over 1800 patients have established that BCI is a standardized, clinically-validated molecular test with clinical utility. These studies demonstrated that BCI quantifies a patient's individualized risk of cumulative (overall 10y), early (0-5y), and specifically late (5-10y) distant recurrence, and predicts responsiveness to and the likelihood of benefit from extended endocrine therapy. BCI can be used to facilitate the selection of those patients likely to benefit, thus potentially sparing those patients unlikely to benefit from unnecessary adverse events and toxicities associated with extended adjuvant endocrine therapy.

Test Description: BCI is a gene expression-based (RT-PCR) assay 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 over 10 years, including a distinct prediction for late recurrence. The BCI Score is derived from an algorithm that incorporates H/I with a set of proliferation-based genes.

BCI Predictive Data Summary: In retrospective studies of 3 prospective randomized trials (Stockholm, TransATAC and MA.17, Table 1; N=1514),[1-3] statistically significant interactions between H/I and endocrine treatment demonstrated the consistent ability of H/I to function as a biomarker for endocrine response.

Table 1: Summary of predictive treatment benefit by H/I categorization

Study Cohort	Treatment	Multivariate analysis	Interaction P value
Stockholm (n=600)[1]	Adjuvant tamoxifen vs untreated	H/I High HR: 0.35 (0.19-0.65); p=0.0005 H/I Low HR: 0.67 (0.36-1.24), p=0.2	0.003
TransATAC (n=665)[2]	Adjuvant anastrozole vs tamoxifen	H/I High HR: 0.51 (0.27-0.97); p=0.04 H/I Low HR: 1.33 (0.65-2.71), p=0.4	0.004
MA.17 (n=249)[3]	Extended letrozole vs placebo	H/I High OR: 0.33 (0.15-0.73); p=0.006 H/I Low OR: 0.58 (0.25-1.36), p=0.21	0.03

Validation in the extended adjuvant setting was conducted using the landmark MA.17 trial in a study designed by the NCIC-CTG to enrich for recurrences as a case-controlled investigation [due to low recurrence rate in the parent trial (3.2%)[5] at termination, and no biorepository]. The analysis included 83 events, representing 31.3% of recurrences in the parent trial. This study demonstrated a statistically significant interaction between H/I and treatment (p=0.03). The reduction in estimated absolute risk of recurrence with extended letrozole was 16.5% for patients with High H/I (p=0.007), and nonsignificant for Low H/I (p=0.35).[3]

BCI Prognostic Data Summary: The BCI assay also provides a prognostic BCI Score, which quantifies an individualized risk of late (>5 years post diagnosis) recurrence as a continuous variable. The BCI Score has been validated in 3 cohorts, including patients treated with either an initial 5 years of adjuvant tamoxifen or anastrozole (n=1193, Table 2).[1,4] These studies consistently demonstrated that BCI stratifies 2 clinical risk groups for late recurrence (Table 2): 1) patients classified as Intermediate or High Risk (36-45% of patients) with similar rates of late distant recurrence; and 2) patients classified as Low Risk (55-64% of patients).

Table 2: **Summary of BCI stratification of risk of late recurrence by study cohort**

	Risk of Recurrence after year 5*		**Hazard Ratio (95% CI) (Int/High Risk vs Low Risk)**
	Low Risk	**Int/High Risk**	
Study Cohort	DRR (95% CI)	DRR (95% CI)	
Stockholm (n=285)[1]	2.8% (0.3% - 5.2%)	8.4% (2.6% - 13.9%)	3.13 (1.02, 9.58)
Multi-institutional (n=312)[1]	2.5% (0.0% - 5.0%)	15.9% (8.9% - 22.3%)	6.96 (2.37, 20.47)
TransATAC (n=596)[4]	3.5% (2.0% - 6.1%)	13.4% (9.3% - 19.0%)	2.94 (1.44-6.01)

DRR, Distant Recurrence Rate
*In patients disease-free after initial 5 years of adjuvant endocrine treatment

The majority of patients (88-93%) in these studies were HER2-negative, and BCI was also strongly prognostic in this clinical subset.[1,4]

Clinical Test Reporting: For clinical assessment beyond 5 years from diagnosis, BCI provides both predictive and risk-stratification test results. The H/I ratio provides information on endocrine responsiveness. The BCI Score provides risk stratification information and can be evaluated in the context of other traditional clinicopathologic factors. When used in conjunction, for example, BCI results comprised of a Low H/I ratio and a Low BCI Score would identify patients adequately treated with 5 years of endocrine therapy, and unlikely to benefit from continued treatment. BCI results comprised of a High H/I ratio and an Intermediate/High BCI Score would identify patients with endocrine responsive disease and a high-risk of late recurrence, who have a high likelihood to benefit from extended adjuvant endocrine therapy.

Finally, we also note that the CMS Molecular Diagnostic Services (MolDX) Program has recently reviewed and issued a positive coverage determination for BCI.

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 (858-587-5884 or cathy.schnabel@biotheranostics.com).

Sincerely,

Catherine Schnabel, PhD
Vice President, Translational Science
bioTheranostics, Inc

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6. Goss PE, et al. JNCI 2005; 1262.
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