

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 Breast Cancer Panel** to update the NCCN Guidelines based on the enclosed data for the **Breast Cancer Index (BCI)** in the evaluation of patients with hormone receptor-positive (HR+), HER2-negative early stage breast cancer to stratify patients by risk of late (post- 5 years from diagnosis) distant recurrence, and to identify patients for likelihood of benefit from extended endocrine therapy.

Specific Changes: Addition of a separate table in section BINV-M, similar in format to that previously added by the NCCN in 2018 for adjuvant chemotherapy decision-making, which summarizes validated multigene assays for extended adjuvant endocrine therapy decision-making.

MULTIGENE ASSAYS FOR CONSIDERATION OF EXTENSION OF ENDOCRINE THERAPY

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk/Likelihood of Extended Endocrine Benefit	Treatment Implications
11-gene assay (Breast Cancer Index; BCI)	Yes (2 gene HoxB13/IL17R [H/I]) Binary (High vs Low likelihood)	Yes (11 gene BCI score) – Individualized risk of late DR in years 5-10 post-diagnosis (High versus Low risk categories)			Low	<ul style="list-style-type: none"> Patients with HR+, HER2-negative, N0 tumors categorized by BCI Score as low risk for late distant recurrence (BCI Score < 5.0825) had a mean distant recurrence risk of 2.5-3.5% in years 5 to 10 post diagnosis in three validation cohorts.^{1,2,3}
						<ul style="list-style-type: none"> Patients with HR+, HER2-negative, N0/N+ tumors categorized by BCI as H/I Low did not significantly benefit from more than 5 years of endocrine therapy in the MA.17 and Trans-aTTom studies.^{4,5}
					High	<ul style="list-style-type: none"> Patients with HR+, HER2-negative N0 tumors categorized by BCI Score as high risk for late distant recurrence (BCI Score > 5.0825) had a mean distant recurrence risk of 8.5-15.9% in years 5 to 10 post diagnosis in three validation cohorts.^{1,2,3}
						<ul style="list-style-type: none"> Patients with HR+, HER2-negative, N0/N+ categorized by BCI as H/I High showed significant benefit from more than 5 years of endocrine therapy in the MA.17 and Trans-aTTom studies.^{4,5} Relative risk reduction was 65% in both the MA.17 and Trans-aTTom studies.

* Residual risk of recurrence after completing primary adjuvant endocrine therapy

Regulatory Status: BCI testing 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: With newly reported Trans-aTTom data, BCI strengthens its evidence level to 1B by Simon and Hayes criteria⁶ for prediction of response to extended endocrine therapy^{4,5} and prognosis of late distant

recurrence^{1,2,3}, providing unique clinical utility to individualize selection and optimize the risk-to-benefit ratio for extended endocrine therapy in patients diagnosed with HR+ early stage breast cancer.

The following articles are submitted in support of the proposed changes:

1. Zhang Y, et al. Breast cancer index identifies early-stage estrogen receptor-positive breast cancer patients at risk for early- and late-distant recurrence. *Clin Cancer Res* 2013;19:4196-205.
2. Sgroi DC, et al. Prediction of late distant recurrence in patients with oestrogen- receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. *Lancet Oncol* 2013;14:1067-76.
3. Sestak I, et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor–positive breast cancer: A secondary analysis of a randomized clinical trial. *JAMA Oncology* 2018;4:545-553.
4. Sgroi DC, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. *J Natl Cancer Inst* 2013;105:1036-42.
5. Bartlett JM, et al. Trans-aTTom: Breast Cancer Index for prediction of endocrine benefit and late distant recurrence (DR) in patients with HR+ breast cancer treated in the adjuvant tamoxifen—To offer more? (aTTom) trial. *Annals of Oncology* (manuscript accepted for publication)
6. Simon RM, et al. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst* 2009;101(21):1446-1452.

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).



Catherine Schnabel, PhD
Chief Scientific Officer
Biotheranostics, Inc.