

**Submitted by:**

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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 identify patients with endocrine-responsive tumor biology who are likely to benefit from extended endocrine therapy, and to stratify patients for risk of late (post-5 years from diagnosis) distant recurrence.

**Specific Changes (one sentence):** Revisions are requested to the BINV-N<sup>7</sup> Table to include 1) changes to the title to add adjuvant extended endocrine therapy 2) a change from “No” to “Yes” for BCI validated Predictive ability and 3) addition of BCI results from the MA.17 and IDEAL studies in the treatment implications (requested changes highlighted in yellow).

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADDITION OF ADJUVANT SYSTEMIC CHEMOTHERAPY <b>OR EXTENDED ENDOCRINE THERAPY</b> TO PRIMARY ADJUVANT ENDOCRINE THERAPY					
ASSAY	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk and Treatment Implications
Breast Cancer Index	Yes (Extended Endocrine Therapy)	Yes			BINV-N(3of4)
Treatment Implications for Gene Expression Assays					
Assay	Recurrence Risk/ Predictive Result		Treatment Implications		
Breast Cancer Index	BCI Low		<ul style="list-style-type: none"> <li>For patients with T1 and T2 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a BCI with low-risk range (0-5), regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0<sup>1-3</sup>.</li> <li>Patients with BCI (H/I) Low demonstrated no significant recurrence prevention benefit from longer duration therapy (RFI) in analyses from the MA.17, Trans-aTTom and IDEAL trials<sup>4-6</sup></li> </ul>		
	BCI High		<ul style="list-style-type: none"> <li>For patients with T1 hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a BCI with high-risk range (5.1-10), demonstrated significant rates of late distant recurrence<sup>3</sup></li> <li>In analyses of the MA.17, Trans-aTTom and IDEAL trials, patients with HR+, T1-T3, N0/N+ disease who had a BCI (H/I) High demonstrated a significant recurrence prevention benefit (RFI; 58%-65% relative risk reduction) from longer duration endocrine therapy<sup>4-6</sup></li> </ul>		

**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 (one sentence):** BINV-N<sup>7</sup> currently includes BCI data from the Trans-aTTom study supporting an extended endocrine therapy indication, which expands the use of gene expression assays beyond adjuvant chemotherapy decision-making indicated by the current title, and thus should be updated for accuracy in the title and predictive fields to reflect the collective evidence for BCI and prediction of extended endocrine benefit in the MA.17<sup>4</sup>, Trans-aTTom<sup>5</sup> and IDEAL<sup>6</sup> studies.

Study Cohort	Relative Risk Reduction		Absolute Benefit (RFI; in H/I High)	Interaction P-Value
	BCI (H/I) High	BCI (H/I) Low		
Treatment: Extended AI vs Placebo after adjuvant TAM				
MA.17 <sup>4</sup> (n=249)	OR: 0.35 (0.16-0.75); p=0.007	OR: 0.68 (0.31-1.52); p=0.350	16.5%	0.030
Treatment: Extended TAM vs Stop after adjuvant TAM				
Trans-aTTom <sup>5</sup> (n=583)	HR: 0.35 (0.15-0.86); p=0.027	HR: 1.07 (0.69-1.65); p=0.768	10.2%	0.012
Treatment: 5y vs 2.5y Extended AI after adjuvant TAM, AI, or TAM/AI sequence				
IDEAL <sup>6</sup> (n=908) Overall  (n=794) Any AI subset	HR: 0.42 (0.21–0.84); p=0.011	HR: 0.95 (0.58-1.56); p=0.835	9.8%	0.045
	HR: 0.34 (0.16–0.73); p=0.004	HR: 0.9 (0.53-1.55); p=0.712	11.8%	0.025

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. Schroeder B, et al. Risk stratification with Breast Cancer Index for late distant recurrence in patients with clinically low-risk (T1N0) estrogen receptor-positive breast cancer. NPJ Breast Cancer. 2017;3:28..
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 Oncol 2019 doi:10.1093/annonc/mdz289
6. Liefers GJ, et al Breast Cancer Index (BCI) Predicts Benefit of 2.5 vs. 5 Years of Extended Endocrine Therapy in HR+ Breast Cancer Patients Treated in the IDEAL Trial. J Clin Onc. 38, no. 15\_suppl (May 20, 2020) 512-512.
7. National Comprehensive Cancer Network. Breast Cancer (Version 5.2020). [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). Accessed August 2, 2020.

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.



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