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NCCN Guidelines Panel: Breast Cancer

On behalf of Biotheranostics Inc., I respectfully request the NCCN Breast Cancer Panel to review the enclosed published data for consideration of the Breast Cancer Index (BCI) test for the molecular assessment of late (post 5 year) distant recurrence risk for patients with hormone receptor-positive (HR+), lymph node-negative breast cancer to aid in decision-making for extended adjuvant endocrine therapy (EET).

Specific Change: Addition of BCI into the NCCN Guideline (BINV-6) for patients with node-negative, HR+ tumors ≥0.5cm, as a complementary gene expression-based prognostic test, to aid in individualized decision-making for EET following completion of adjuvant endocrine treatment. The specific request is a component or footnote of the clinical guideline as follows: "**The Breast Cancer Index prognostic multigene assay may be considered to help assess residual risk of late distant recurrence (post 5 year) after completion of 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: BCI has established Level 1b evidence[1] as a significant prognostic factor for risk of late distant recurrence,[2,3] and provides a standardized assessment of individualized risk in patients with node-negative, HR+ breast cancer that improves over clinicopathologic risk factors. BCI identifies patient subsets with a limited risk of late distant recurrence, such that continuing endocrine therapy beyond year 5 would be unlikely to substantially reduce the risk of recurrence. BCI also identifies patients with clinically favorable prognosis (eg, T1N0) that have higher risk of late distant recurrence based on tumor biology, and may benefit from longer durations of endocrine therapy.

Test Description: BCI is a gene expression-based (RT-PCR, 11 genes) assay performed on RNA isolated from formalin-fixed paraffin-embedded primary tumor tissue for patients with Stage I-IIa, node-negative, HR+ breast cancer. The BCI assay reports both a prognostic result (individualized risk of cumulative [0-10y] and late [5-10y] distant recurrence based on a continuous model)[2,3] and a predictive result (categorical, high vs low likelihood of benefit from extended endocrine therapy). The prognostic component has been validated in 3 studies, including 2 prospective-retrospective studies (see below). Prediction of extended endocrine response was validated in MA.17,[4] with additional confirmatory studies ongoing.

Background: Several landmark studies, including the newly-reported MA.17R randomized trial, have demonstrated a reduced risk of late recurrence with EET.[5-9] However, across studies, only a modest proportion of patients benefited from EET (3-6% absolute benefit; number needed to treat [NNT] between 20-30 to prevent 1 recurrence), and risk of several serious toxicities was increased. The absolute benefit of EET was even smaller in prevention of distant recurrences (with NNTs as high as 90 to prevent 1 recurrence), and in node-negative subsets. As such, balancing risk vs benefit of therapeutic interventions is important for these patients and their long term health outcomes, and individualized risk assessment plays a critical role.

The 2014 ASCO Clinical Practice Guidelines[10] endorse consideration of EET, but highlight specifically that: "patients with favorable prognosis tumors may experience more risk than benefit with extended adjuvant treatment" and that "considerations of benefit and risk on the basis of stage and the adverse effects experienced by a given patient may help clinical teams make individualized recommendations on the appropriateness of ongoing treatment for a specific woman." Thus, physicians are urged to consider prolonged durations of endocrine therapy without specific guidance as to which patients are most appropriate candidates based on individualized factors. Traditional clinicopathologic factors are prognostic for risk of late recurrence; however, resolution is limited. Most recently, an EBCTCG meta-analysis showed that clinically low risk patients (eg, T1N0) still have a considerable risk of late recurrence.[11] Genomic interrogation has been shown to provide increased prognostic resolution and individualized risk assessment where traditional clinicopathologic factors are limited.

Data Summary: BCI has been demonstrated to be a significant prognostic factor for risk of late (>5 year) recurrence in 3 validation studies (N=1193), including 2 prospective-retrospective studies completed using archived tissue from prospective randomized controlled trial cohorts (Level 1b evidence[1]) as well as an independent multi-institutional cohort.[2,3] BCI consistently identified a significant subset of node-negative, HR+ patients (~60%) at low risk for late distant recurrence (Table 1; N=1193).[2,3] In the TransATAC study, patients classified as BCI Low Risk had a 3.5% risk of late recurrence (Figure 1A). In the subset of HER2- patients, the late recurrence rate was 2.8%. In the Stockholm study,

patients classified as BCI Low Risk had a 2.8% rate of late recurrence between years 5-10, and a 1.9% rate of recurrence between years 10-15 (Figure 1B).

Together, these data demonstrate that in the subset of node-negative ER+ patients who are disease-free at 5 years post-diagnosis, BCI consistently identified patients with a low risk of late distant recurrence. Given the limited risk, extending endocrine therapy is unlikely to substantially reduce risk further for most patients; thus, these patients could potentially be spared the adverse events and toxicities associated with extended adjuvant endocrine therapy. Conversely, BCI also identifies patients that may have a clinically favorable prognosis (eg, T1N0) but are at high risk of late distant recurrence based on tumor biology, and may be more likely to benefit from prolonging the duration endocrine therapy.

Figure 1. Late Distant Recurrence Risk (Post 5 Years) for BCI Low and BCI Intermediate/High Risk Groups in A) TransATAC cohort[3] or B) Stockholm cohort[2]
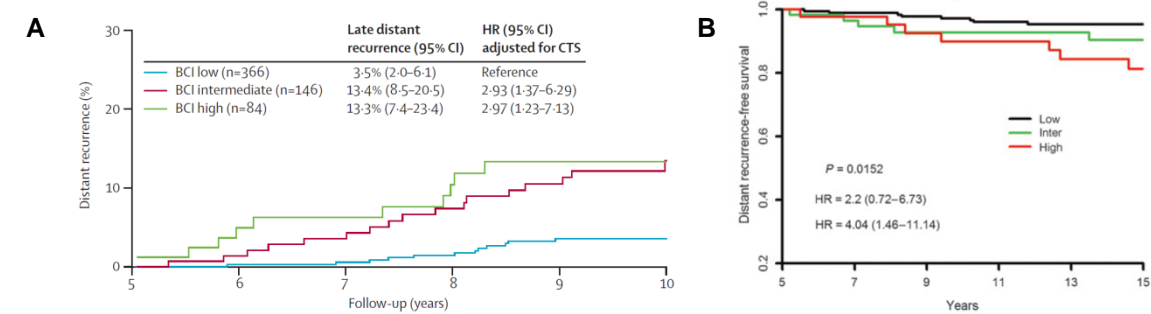

Table 1. Late (5-10 year) Distant Recurrence Rates for BCI Low vs BCI Intermediate/High Across Cohorts

| | Risk of Recurrence From Year 5-10* | | Hazard Ratio (95% CI) (Int/High-Risk vs Low) |
	Low-Risk	Intermediate/High-Risk	
Study Cohort	DRR (95% CI)	DRR (95% CI)	
Stockholm (n=285)[2]	**2.8%** (0.3% - 5.2%)	8.4% (2.6% - 13.9%)	3.13 (1.02, 9.58)
Multi-institutional (n=312)[2]	**2.5%** (0% - 5.0%)	15.9% (8.9% - 22.3%)	6.96 (2.37, 20.47)
TransATAC (n=596)[3]	**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

We gratefully acknowledge our investigators from several NCCN centers. We also highlight for the committee that since its commercial launch in 2014, BCI has been ordered by more than 1,400 medical oncologists (including 17 NCCN Member Institutions) for more than 12,000 women. The CMS Molecular Diagnostic Services (MolDX) Program and several private insurers have issued positive coverage determinations for BCI. Finally, we note that both ASCO[12] and NCCN[13] have acknowledged the clinical validity and clinical utility of BCI for use in risk assessment for adjuvant systemic therapy decision-making.

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).

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