Predictive testing for selection of patients for extended endocrine therapy: clinical utilization of Breast Cancer Index (BCI) in early-stage, ER+, LN- Breast cancer

Authors: Stephen C. Malamud, MD, Brock E. Schroeder, PhD, Theresa N. Operaña, PhD, Catherine A. Schnabel, PhD

Highlights:

- In analyses of major extended endocrine therapy (EET) trials, clinicopathologic factors did not predict benefit from EET; thus, there has been an unmet need to help identify patients most likely to benefit from EET
- This study examined the clinical utility and utilization of Breast Cancer Index[SM] (BCI) in clinical practice, and its ability to identify patients likely to benefit from EET in an otherwise low risk population
- 853 consecutive cases submitted for Breast Cancer Index clinical testing from lymph node negative breast cancer patients were investigated
- Although the majority of Breast Cancer Index testing occurred between 4-6 years post diagnosis, 25% of testing took place between year 2-4 and 18% more than 6 years post diagnosis
- A subset analysis was performed in 328 patients with low clinicopathologic risk profiles (node-negative, T1, Grade 1-2, HER2-)
- 23% of this subset were classified by Breast Cancer Index as high risk and high likelihood to benefit from EET; these patients should be considered candidates for EET despite their low clinicopathologic risk profile

Breast Cancer INDEX[SM]

For Questions, Visit www.BreastCancerIndex.com
Email Medical Affairs at: medicalaffairs@biotheranostics.com
Call: 1-877-886-6739

Intended Uses and Limitations The Breast Cancer Index (BCI) Risk of Recurrence & Extended Endocrine Benefit Test is intended for use in patients diagnosed with estrogen receptor-positive (ER+), lymph node-negative (LN-) or lymph node positive (LN+; with 1-3 positive nodes) early-stage, invasive breast cancer, who are distant recurrence-free. BCI provides: 1) a quantitative assessment of the likelihood of both late (post-5 years) and overall (0-10 year) distant recurrence following an initial 5 years of endocrine therapy (LN- patients) or 5 years of endocrine therapy plus adjuvant chemotherapy (LN+ patients), and 2) prediction of likelihood of benefit from extended (>5 year) endocrine therapy. BCI results are adjunctive to the ordering physician's workup; treatment decisions require correlation with all other clinical findings. This test was developed and its performance characteristics determined by Biotheranostics, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration. This test is used for clinical purposes. It should not be regarded as investigational or for research. How this information is used to guide patient care is the responsibility of the physician. Biotheranostics is certified under the Clinical Laboratory Improvement Amendments of 1988 to perform high complexity clinical laboratory testing.

Biotheranostics, Inc. | 9640 Towne Centre Drive | Suite 200 San Diego, CA 92121 | Biotheranostics.com US and International: (858) 587-5870 | Fax: (800) 266-9607 |
Client Services: (877) 886-6739 BREAST CANCER INDEX is a registered service mark of Biotheranostics, Inc.

Predictive testing for selection of patients for extended endocrine therapy: clinical utilization of Breast Cancer Index (BCI) in early-stage, ER+, LN- breast cancer

Malamud SC[1], Schroeder BE[2], Operaña TN[2], Schnabel CA[2]

[1]Beth Israel Medical Center, New York, NY; [2]bioTheranostics, Inc., San Diego, CA

INTRODUCTION

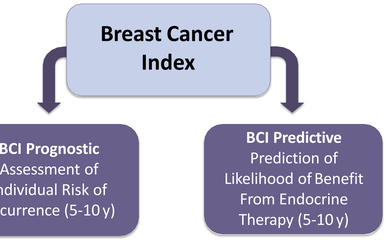
- Randomized trials have demonstrated significant but modest (3-5%) benefit from extended (10y) endocrine therapy (EET) vs 5y in patients with early stage ER+ breast cancer.[1-4]
- Clinical practice guidelines have speculated on the risk vs benefit of EET in patients with a low clinicopathologic risk profile.[5]
- In analyses of major EET trials, clinicopathologic factors did not predict benefit from EET;[2,3,8] thus, there has been an unmet need to help identify patients most likely to benefit from extended therapy.
- Breast Cancer Index (BCI) is a gene expression-based test that is prognostic for risk of late (> 5y) recurrence[6,7] and predictive of endocrine therapy benefit in early-stage hormone receptor-positive breast cancer.[6,8,9]
- This study examined the clinical utility and utilization of BCI in clinical practice, and its ability to identify patients likely to benefit from EET in an otherwise low risk population.

MATERIALS AND METHODS

- Consecutive cases submitted for BCI clinical testing from lymph node negative breast cancer patients were investigated (N = 853).
- Clinical and pathologic information including age, tumor grade, tumor size, and HER2 status were abstracted from pathology reports.
- Patient characteristics, clinician testing patterns, and clinical results were analyzed descriptively.
- A subset analysis was performed in patients with low clinicopathologic risk profiles (node-negative, T1, Grade 1-2, HER2-).

BACKGROUND

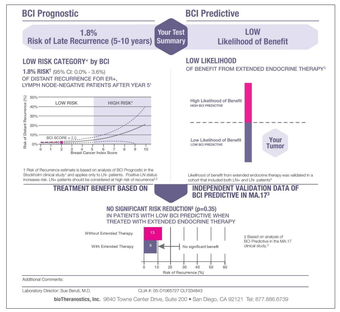
Figure 1. BCI Provides Two Results (Prognostic and Predictive)



- Based on algorithmic combination of MGI (Proliferation Pathway) and H/I (Estrogen Signaling Pathway)
- Provides individualized risk of late recurrence and risk category (Low Risk <4.8%, High Risk >4.8%)
- Quantitative molecular assessment of estrogen signaling pathways (H/I)
- Provides binary result: High or Low likelihood of benefit from EET

MGI Genes: BUB1B, CENPA, NEK2, RACGAP1, RRM2 H/I: HoxB13/IL17BR

BCI Results



Low Risk **Low Likelihood of Benefit**	**High Risk** **Low Likelihood of Benefit**
Low Risk **High Likelihood of Benefit**	**High Risk** **High Likelihood of Benefit**

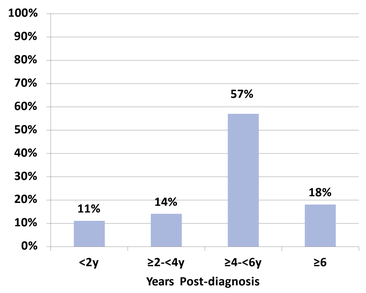
RESULTS

Table 1. Patient Characteristics

Patient Characteristics (N=853)		
Age	Mean	57 y
	< 50	28%
	≥ 50	72%
Tumor Grade	1	29%
	2	52%
	3	19%
Tumor Size	≤ 1 cm	26%
	> 1 - ≤ 2 cm	49%
	> 2 - ≤ 5 cm	23%
	> 5 cm	2%
HER2	Negative	89%
	Positive	11%

- Majority of tumors were small (≤ 2 cm), low to intermediate grade, and HER2-

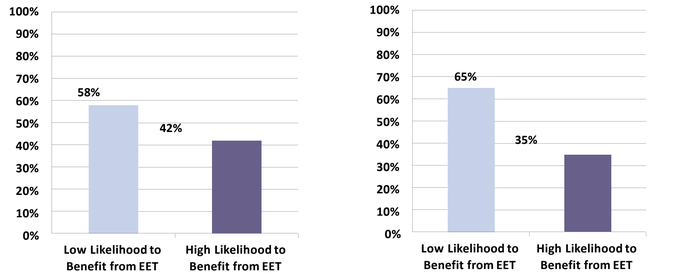
Figure 2. Timing of BCI Utilization Post-diagnosis



- The majority of BCI tests ordered were for patients between 4 to 6 years post diagnosis

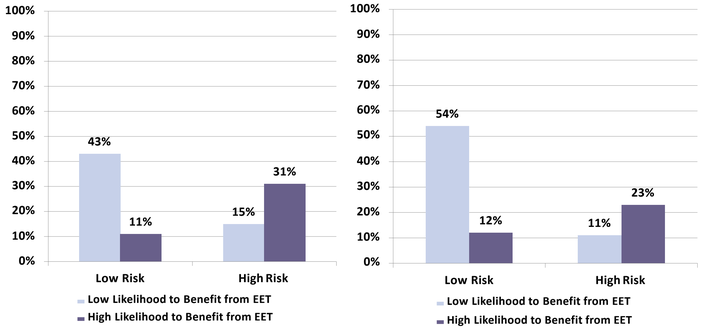
RESULTS

Figure 3. Patient Stratification by BCI Predictive



- BCI Predictive identified the majority of patients (58%) as having a low likelihood of benefit from EET vs 42% with a high likelihood of benefit (Fig. 3A); these proportions are similar to validation cohorts.
- In the subset of patients (n=321) with a low clinicopathologic risk profile, BCI Predictive identified a substantial minority of patients (35%) as having a high likelihood of benefit from EET (Fig. 3B).

Figure 4. Stratification by BCI Predictive and BCI Prognostic for Late Recurrence



- BCI identified 43% of patients as having low risk for late distant recurrence and low likelihood of benefit from EET vs 31% with high risk for late recurrence and high likelihood of benefit from EET (Fig. 4A).
- In a subset of patients with low clinicopathologic risk factors, BCI identified 23% of patients as having high risk for late distant recurrence and high likelihood of benefit from EET (Fig. 4B).

Case Study 1	Case Study 2
▪ 49 y Female ▪ Premenopausal ▪ Diagnosed with IDC in 2007	▪ 51 y Female ▪ Premenopausal ▪ Diagnosed with IDC in 2007
Tumor ▪ ER+/ PR-/ HER2- ▪ 1.3 cm ▪ Intermediate grade ▪ LN- ▪ Recurrence Score =25, Inter. Risk	Tumor ▪ ER+/ PR+/ HER2- ▪ 1.4 cm ▪ Intermediate grade ▪ LN- ▪ Recurrence Score =17, Low Risk
Adjuvant Treatment ▪ Tamoxifen	Adjuvant Treatment ▪ Tamoxifen
Patient Side Effects ▪ Weight gain ▪ Sexual side effects	Patient Side Effects ▪ Weight gain
BCI Results ▪ BCI Prognostic= 4.2% Risk (Low) ▪ BCI Predictive= Low Likelihood to Benefit from EET	BCI Results ▪ BCI Prognostic= 10.6% Risk (High) ▪ BCI Predictive= High Likelihood to Benefit from EET
Treatment Decision ▪ Stop endocrine therapy	Treatment Decision ▪ Continue endocrine therapy

CONCLUSIONS

- The results of this large retrospective analysis demonstrate the clinical utility of BCI to stratify patients based on risk of late recurrence and likelihood of benefit from EET.
- The most common utilization of BCI was between 4-6y post-diagnosis; however, earlier (<4y) and later (>6y) utilization suggests clinical utility for managing patient expectations regarding duration of endocrine therapy and for revisiting previous decisions regarding EET.
- BCI identified a majority of patients as having a low likelihood of benefit from EET. Based on results from published studies, these patients may be adequately treated with 5 years of endocrine therapy.
- Notably, in the subset of patients that would be considered low risk by clinicopathologic criteria, BCI identified a substantial minority of patients as having a higher risk of recurrence and a high likelihood of benefit from EET; these patients should be considered candidates for EET, despite their clinicopathologic risk profile.

REFERENCES

1. Goss PE et al., N Engl J Med 2003;349.
2. Goss PE et al, J Natl Cancer Inst 2005;97:1262–71
3. Davies C et al., Lancet. 2013;381(9869):805-16.
4. Gray et al., J Clin Oncol 31, 2013 (suppl; abstr 5).
5. Burstein et al. J Clin Oncol. 2014 Jul 20;32(21):2255-69.
6. Zhang Y et al. Clin Cancer Res. 2013;19:4196–205.
7. Sgroi DC et al. Lancet Oncol. Oct 2013; 14:1067–1076.
8. Sgroi DC et al. J Natl Cancer Inst. 2013;105:1036–42.
9. Sgroi, et al, Cancer Res 2012;72 (Suppl.): Abstract nr P2-10-5