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An optimized Breast Cancer Index node-positive (BCIN+) prognostic model for late distant recurrence in patients with hormone receptor positive (HR+) node positive breast cancer

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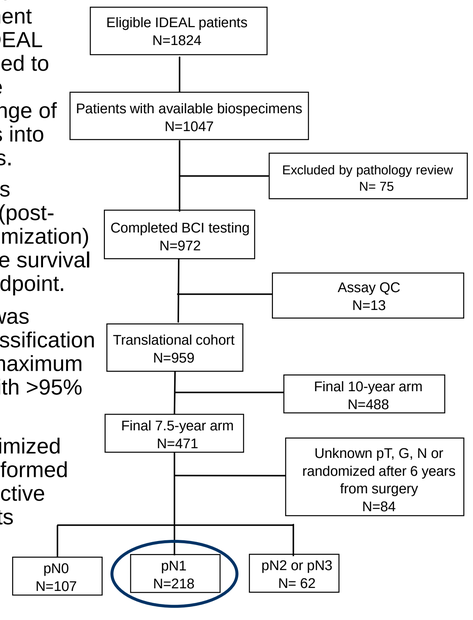
INTRODUCTION

- Breast Cancer Index (BCI) is a validated gene expression-based assay that integrates the molecular grade index (MGI) and the two-gene ratio HOXB13/IL17BR (H/I), that evaluate tumor proliferation and estrogen signaling, respectively.[1-4]
  - Integration of MGI and H/I generates a prognostic BCI score that significantly predicts risk of overall (10y), early (0-5y), and late (≥5y) distant recurrence (DR) in HR+, node-negative (N0) and node-positive (N1) breast cancer.
    - The N1 prognostic model (BCIN+) integrates tumor size and grade.
  - The H/I ratio is the predictive component of BCI and has been shown to predict endocrine response across various treatment regimens.
- The current prognostic model, BCIN+, was trained in the Trans-ATAC (Arimidex, Tamoxifen, Alone or in Combination) cohort, which randomized patients at the time of diagnosis to evaluate primary adjuvant anastrozole versus tamoxifen.[5]
- The IDEAL (Investigation on the Duration of Extended Letrozole) trial randomized patients that completed 5 years of endocrine therapy and compared additional 5 vs 2.5y of extended letrozole providing a cohort that specifically evaluated late DR.
- The aim of the current study was to specifically evaluate prognostic performance of BCIN+ in a late DR cohort.

METHODS

- Patients with 1 to 3 positive nodes (N1) randomized within 6 years from surgery in the 7.5-year endocrine treatment arm of the translational IDEAL cohort (**Figure 1**) were used to examine cut-points for the BCIN+ model across a range of 0 to 10 to classify patients into Low- and High-risk groups.
- Kaplan-Meier analysis was used to calculate the 15y (post-diagnosis, 10y post-randomization) late distant recurrence free survival (DRFS) as the primary endpoint.
- The BCI assay cut-point was selected based on the classification of a Low-risk group with maximum number of patients and with >95% 15y late DRFS.
- Initial validation of the optimized prognostic model was performed in an institutional retrospective cohort from Massachusetts General Hospital (MGH) using Cox proportional hazards regression.

Figure 1. IDEAL translational cohort 7.5-year arm N1 patient flow.



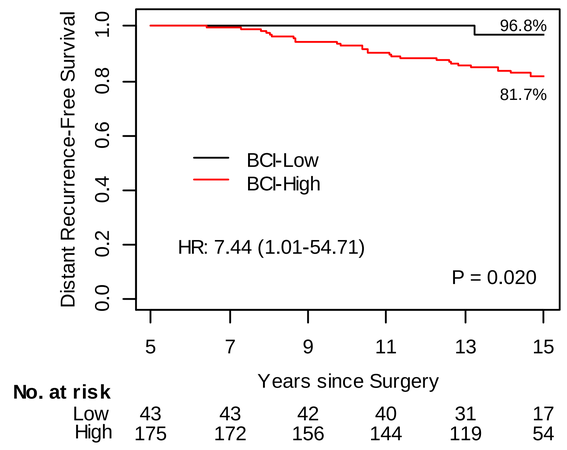
RESULTS

Table 1. Patient Characteristics

	IDEAL N1 (N=218)	MGH N1 (N=349)
Age at surgery		
<50	64 (29%)	127 (36%)
≥50	154 (71%)	222 (64%)
pT stage		
pT1	120 (55%)	231 (66%)
pT2	89 (41%)	109 (31%)
pT3	9 (4%)	9 (3%)
Grade		
1	51 (24%)	70 (20%)
2	112 (51%)	201 (58%)
3	55 (25%)	78 (22%)
Tumor type		
Ductal	174 (80%)	303 (87%)
Mixed	0 (0%)	7 (2%)
Lobular	30 (14%)	39 (11%)
Other	14 (6%)	0 (0%)
ER		
Positive	211 (97%)	345 (99%)
Negative	7 (3%)	4 (1%)
PR		
Positive	180 (83%)	322 (92%)
Negative	33 (15%)	26 (8%)
Unknown	5 (2%)	1 (0%)
HER2		
Positive	19 (9%)	41 (12%)
Negative	75 (34%)	226 (65%)
Unknown	124 (57%)	82 (23%)
Prior endocrine therapy		
5-year TAM	15 (7%)	143 (41%)
5-year AI	60 (28%)	64 (18%)
TAM → AI	143 (65%)	142 (41%)
Prior chemotherapy		
Yes	141 (65%)	277 (80%)
No	77 (35%)	71 (20%)
Unknown	0 (0%)	1 (0%)
Distant Recurrence	30 (14%)	38 (11%)

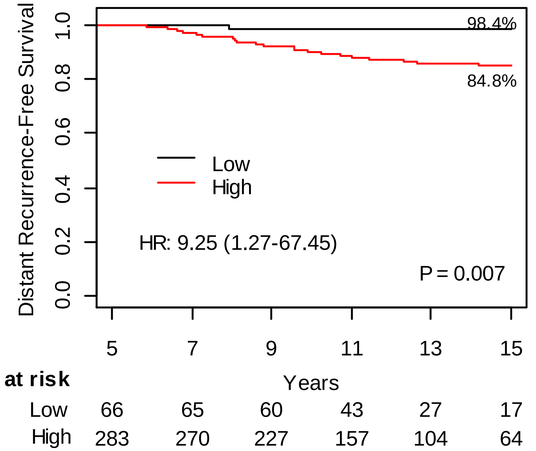
- Of the 218 N1 IDEAL patients included, 71% were ≥ 50y, 55% had T1 tumors, and 51% were grade 2 (**Table 1**).

Figure 2. Optimized BCIN+ in IDEAL N1 Cohort



- A cut-point of 1.8 was selected to ensure >95% 15y late DRFS for BCI-Low risk group.
- In the optimization cohort, 20% patients were classified as BCIN+ Low-Risk with 15-year late DRFS 96.8% (HR: 7.44, 95% CI: 1.01-54.71; p=0.020) (**Figure 2**).

Figure 3. Validation of Optimized BCIN+ in MGH N1 Cohort



- In the validation cohort, the BCIN+ model with an optimized cut-point was significantly prognostic for late DR (HR: 9.25, 95% CI: 1.27-67.45; p=0.007) (**Figure 3**).
- 19% patients were classified as BCIN+ Low-Risk with 15-year risk of late DRFS 98.4% (**Figure 3**).

CONCLUSIONS

- A new optimized cut-point of BCIN+ scores was identified for node positive patients using the IDEAL N1 subset.
- The cut-point was chosen to ensure the 15-year risk of late DR was greater than 95% (96.8% in IDEAL N1).
- The cut-point was validated in the independent MGH N1 cohort for late DR.
- Additional studies in randomized extended endocrine trial N1 cohorts are required for further validation of this BCIN+ model optimized for late DR.

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AUTHOR DISCLOSURES, FUNDING, AND CONTACT INFORMATION

GJL: Consultant/advisor: Biotheranostics, Inc.**;** Research funding: Biotheranostics, Inc. **YZ, KT**: Patents, royalties, other intellectual property: Biotheranostics, Inc.; Stock and other ownership interests: Biotheranostics, Inc.; Employment: Biotheranostics, Inc.; Travel, accommodations, expenses: Biotheranostics, Inc. **JW:** Stock and other ownership interests: Biotheranostics, Inc.; Employment: Biotheranostics, Inc.; Travel, accommodations, expenses: Biotheranostics, Inc. **DCS:** Consultant/advisor: Merrimack Pharmaceuticals; Patents, royalties, other intellectual property: Biotheranostics, Inc. **CAS:** Patents, royalties, other intellectual property: Biotheranostics, Inc.; Stock and other ownership interests: Biotheranostics, Inc.; Leadership: Biotheranostics, Inc.; Employment: Biotheranostics, Inc. Travel, accommodations, expenses: Biotheranostics, Inc. **IN, HP, EMKK, MDC, CV:** Nothing to disclose.

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