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A Breast Cancer Index (BCI) prognostic model for N0 HR+ breast cancer optimized for late distant recurrence

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INTRODUCTION

- Breast Cancer Index (BCI) is a validated multigene assay that reports both predictive and prognostic results as an aid in clinical decision-making for extended endocrine therapy in hormone receptor positive (HR+) breast cancer.[1-4]
- BCI integrates two biomarker panels to report both a predictive and prognostic result:
  - The molecular grade index (MGI) is a 5-gene signature that evaluates tumor proliferation, while the ratio of HOXB13/IL17BR (H/I) evaluates estrogen signaling.
  - Integration of MGI and H/I yields the prognostic BCI score, which quantifies the risk of overall (0-10y), and late (5-10y) distant recurrence (DR).
  - The predictive component of BCI is the H/I ratio, which has been shown to predict endocrine response across different treatment regimens.
- The BCI N0 prognostic model was trained in the STO-3 Stockholm trial with patients who were randomized at the time of diagnosis to compare 5y primary adjuvant tamoxifen vs untreated.[5,6]
- The current study evaluates the BCI prognostic model in a late DR population of HR+ breast cancer to determine potential optimization.
  - The model was optimized using N0 patients in the 5-year arm from the Trans-aTTom trial, who remained disease free after having completed at least 4 years of adjuvant tamoxifen therapy.
  - The optimized model was then validated in a multi-institutional cohort (from MGH and UPMC) to evaluate the performance of the model.

METHODS

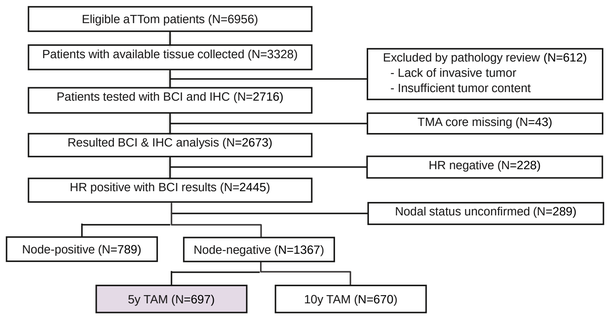
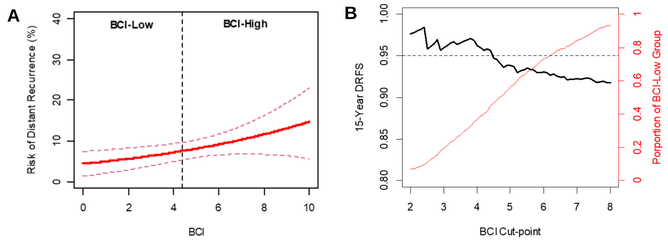


Figure 1. Trans-aTTom case flow.

- Patient data from the 5-year arm of the N0 subset of the Trans-aTTom cohort (n=697) were used to evaluate the current BCI model.[5,6]
- Optimization of the BCI model was performed as follows:
  - Patients were classified into BCI-Low and BCI-High risk groups with varying cut-points.
  - Kaplan-Meier analysis was used to determine 15y distant recurrence-free survival (DRFS).
  - The optimized cut-point was chosen to ensure a 15y DRFS of >95% for patients classified as BCI-Low risk.
- The performance of the optimized cut-point was then validated for prognostication of late DR in a multi-institutional (MGH and UPMC) cohort.
- 312 multi-institutional (MGH and UPMC) patients (47% <55y, 67% T1, 62% grade 2) were included in the validation set.

RESULTS

Figure 2. Trans-aTTom continuous risk curve and optimization of BCI cut-point.

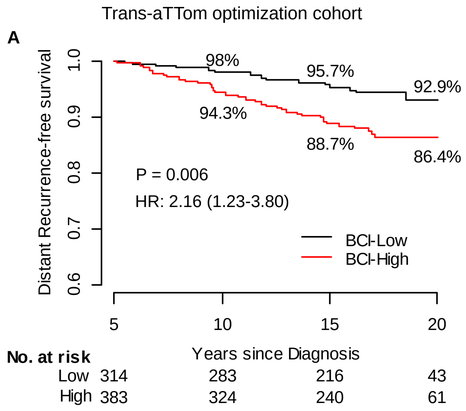


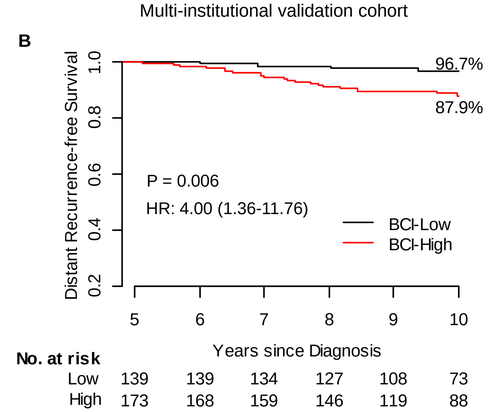
- BCI, as a continuous variable, was significantly prognostic for late DR (HR: 1.14, 95% CI: 1.00-1.28, P = 0.043).
- Risk of DR increases linearly as BCI score increases.
- A cut-point of 4.4 was chosen to ensure >95% 15y late DRFS for the group designated as BCI-Low risk.

	Trans-aTTom (n=697)	Multi-institutional (n=312)
Age		
<50	55 (8%)	97 (31%)
50-59	210 (30%)	102 (33%)
60-69	239 (34%)	77 (25%)
≥70	193 (28%)	36 (11%)
Tumor Size		
T1	492 (71%)	210 (67%)
T2	150 (22%)	93 (30%)
T3	4 (1%)	9 (3%)
Unknown	51 (7%)	---
Histological Grade		
Grade I	162 (23%)	76 (24%)
Grade II	307 (44%)	193 (62%)
Grade III	118 (17%)	43 (14%)
Unknown	110 (16%)	---
Distant recurrence	60 (9%)	31 (10%)

Table 1. Clinicopathological characteristics of Trans-aTTom HR+ N0 cohort and the multi-institutional cohort.

Figure 3. Stratification of patients into BCI-Low and BCI-High risk groups following optimization of the N0 prognostic model for late DR.





- 45% of Trans-aTTom N0 patients were classified as BCI-Low risk with a 15y late DR risk of 95.7%
- At a median follow-up of 10y and 20y, DFRS was 98.0% and 92.9% for BCI-Low risk patients, and 94.3% and 86.4% for BCI-High risk patients, respectively.
- BCI using the new assay cut-point optimized for late recurrence (BCI = 4.4) was significantly prognostic for late DR (HR 4.00; 95% CI: 1.36-11.76; P = 0.006) and classified:
  - 45% of patients as BCI-Low risk with a 10y late DRFS of 96.7%
  - 55% of patients as BCI-High had a 10y late DRFS of 87.9%

Table 2. Summary of 10-, 15-, and 20y late DRFS for the optimization (Trans-aTTom) and validation (multi-institutional) cohorts.

Cohorts	BCI Risk Groups	10y late DRFS (95% CI)	15y late DRFS (95% CI)	20y late DRFS (95% CI)
Trans-aTTom (n=697)	BCI-Low	98.0% (96.4-99.6%)	95.7% (93.3-98.1%)	92.9% (89.3-96.8%)
	BCI-High	94.3% (91.9-96.7%)	88.7% (85.3-92.2%)	86.4% (82.6-90.4%)
Multi-institutional (n=312)	BCI-Low	96.7% (93.6-99.9%)		
	BCI-High	87.9% (82.8-93.3%)		

CONCLUSIONS

- In the current study, a BCI prognostic model for N0 patients was optimized with an adjusted assay cut-point specifically for late DR (post-5 years from diagnosis) in patients that have completed at least 4 years of primary adjuvant endocrine therapy in the aTTom trial.
- Independent validation of this model in a multi-institutional cohort demonstrated that BCI was significantly prognostic for late DR for patients who were DR-free for 5 years.
- Additional studies in randomized controlled trials of extended endocrine therapy and/or late recurrence are planned to further validate this optimized BCI N0 model.

REFERENCES

1. Sgroi DC et al. *Lancet Oncol.* 2013;14:1067-76. **2**. Zhang Y, et al. *Clin Cancer Res.* 2013;19:4196-4205. **3**. Sanft T et al. *Breast Cancer Res Treat*. 2015;154(3):533-41. **4**. Sgroi DC et al. *J Natl Cancer Inst.* 2013;105:1036-1042. **5.** Bartlett JMS et al. *Ann Oncol*. 2019;30(11):1776-1783. **6.** Bartlett JMS et al. SABCS 2019. **7.** Jerevall et al. *Br J Cancer*. 2011:104:1762-1769.

AUTHOR DISCLOSURES

JMSB: Honoraria: Biotheranostics, Inc., NanoString Technologies, Oncology Education, MedcomXchange Communications, Inc.; Consultant/advisor: Biotheranostics, Inc**.,** BioNTech AG, Insight Genetics, Inc., oncoXchange/MedcomXchange Communications, Inc., Pfizer, Rna Diagnostics, Herbert Smith French Solicitors; Research funding: Biotheranostics, Inc., Agendia, Genoptix, NanoString Technologies, Stratifyer GmbH, Thermo Fisher Scientific; Patents, Royalties, Other Intellectual Property: Jan 2017: Methods and Devices for Predicting Anthracycline Treatment Efficacy, US utility – 15/325,472; EPO – 15822898.1; Canada – not yet assigned, Jan 2017: Systems, Devices and Methods for Constructing and Using a Biomarker, US utility – 15/328,108; EPO – 15824751.0; Canada – not yet assigned, Oct 2016: Histone gene module predicts anthracycline benefit, PCT/CA2016/000247, Dec 2016: 95-Gene Signature of Residual Risk Following Endocrine Treatment, PCT/CA2016/000304, Dec 2016: Immune Gene Signature Predicts Anthracycline Benefit, PCT/CA2016/000305, June 2020: Use of Molecular Classifiers to Diagnose, Treat and Prognose Prostate Cancer, US Provisional 63/040.692, Disclosure Name: A Molecular Classifier for Personalized Risk Stratification for Patients with Prostate Cancer, Date: 21/08/2019; Travel, Accommodations, Expenses: Biotheranostics, Inc., NanoString Technologies, Inc., Breast Cancer Society of Canada. **YZ, KT**: Patents, royalties, other intellectual property: Biotheranostics, Inc.; Stock and other ownership interests: Biotheranostics, Inc.; Employment: Biotheranostics, Inc.; Travel, accommodations, expenses: Biotheranostics, Inc. **AMB:** Consultant/Advisor: AstraZeneca, Pfizer, Eli Lilly, Novartis, Roche, Daiichi Sankyo, Myriad, Agendia, 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. **DWR:** Honoraria: Daiichi Sankyo, Eli Lilly, Novartis, Pfizer, Roche; Consultant/Advisor: Genomic Health, MSD Oncology; Research Funding: Biotheranostics, Inc., Celgene, Roche; Travel, Accommodations, Expenses: Daiichi Sankyo, Eisai, Novartis, Pfizer. **IA, TP, SJP:** Nothing to disclose.

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