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CLINICAL TRIAL

Discrepancy in risk assessment of hormone receptor positive early-stage breast cancer patients using breast cancer index and recurrence score

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Abstract

Purpose A recent comparison of the prognostic accuracy of Breast Cancer Index (BCI) and the Recurrence Score (RS) showed that BCI was more precise than RS. BCI identified a subset of RS low and intermediate risk patients with clinically relevant elevated rates of distant recurrences (DR). The current study analyzed the correlation of BCI and RS risk classification to clinical and pathological parameters and further examined the re-categorization between the two risk group indices in a multi-institutional cohort of hormone receptor positive (HR+) breast cancer patients.

Methods 560 women with HR+, lymph node-negative breast cancer who underwent testing with RS as part of their routine clinical care were included in the final analysis. Individual risk was assessed using predefined categories of RS and BCI (Low, Intermediate and High, respectively). Correlations between BCI, RS, and standard clinical-pathological prognostic factors were examined, and re-categorization of risk groups between BCI and RS was analyzed.

Results An overall significant association between histological tumor grade and RS or BCI was observed with high-grade tumors more prevalent among RS and BCI high-risk patients. The invasive ductal carcinoma histologic subtype was associated with 98% and 93% of high-risk RS and BCI cases, respectively. The invasive lobular subtype accounted for 0% and 6% of high-risk RS and BCI cases, respectively. A poor agreement between the two biomarker risk group indices was demonstrated with more than 51% of the total cohort stratified differently between BCI and RS. As compared with RS, BCI stratified fewer patients into the intermediate-risk group (29% vs. 39%, BCI and RS, respectively) and more patients into the high-risk group (19% vs. 7%, BCI and RS, respectively). Subsets of both RS low- and intermediate-risk patients were identified by BCI as high risk.

Conclusions In this clinical series, BCI and RS risk groups demonstrated a significant association with histological tumor grade. BCI showed a modest correlation with tumor size and no correlation with age, while RS showed no correlation with tumor size or age. Compared with RS, BCI classifies fewer intermediate risk patients, identifies subsets of low and intermediate RS risk patients as high-risk, and provides distinct individualized risk assessment for patients with early-stage breast cancer.

Keywords Breast cancer · Risk prediction · Prognosis · Biomarkers

Abbreviations

BCI	Breast Cancer Index
RS	OncotypeDx recurrence score
DR	Distant recurrence
HR+	Hormone receptor positive
FFPE	Formalin-fixed paraffin-embedded
H:I	HOXB13:IL17BR
MGI	Molecular grade index
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
HER2	Human epidermal growth factor receptor 2

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Introduction

The hormone receptor positive (HR+) subtype accounts for the majority of all breast cancers diagnosed worldwide, and this category also represents the single largest subgroup of breast cancer patients requiring therapeutic intervention [1]. Standard adjuvant systemic treatment options for HR+ breast cancer patients include hormonal therapy alone, chemotherapy with hormonal therapy, and lastly, chemotherapy with hormonal and anti-HER2 (human epidermal growth factor receptor 2) therapy for the HER2+ subset of ER+ patients [2]. Although clinical trial data demonstrate that chemotherapy adds some additional benefit beyond hormonal therapy, it is estimated that more than 60% of HR+ patients are exposed to chemotherapy toxicities with little or no clinical benefit [3, 4]. Currently, the selection of systemic therapy is based upon the estimate of potential responsiveness and risk of recurrence, both of which are traditionally assessed using clinical-pathological parameters such as age, tumor size and grade, and lymph node, estrogen receptor, progesterone receptor and HER2 status [5, 6]. Unfortunately, these factors fail to accurately stratify HR+ breast cancers according to their clinical behavior or therapeutic response, and hence, the identification of patients who will or will not benefit from the additional therapy can be limited.

Over the past decade, translational research has identified multiple molecular biomarkers that demonstrate superior prognostic and treatment predictive performance over traditional clinical-pathological parameters [7–19]. As evidenced by the ASCO (American Society of Clinical Oncology) and NCCN (National Comprehensive Cancer Network) endorsements [20], the OncotypeDx Recurrence Score (RS) has emerged in the United States as the preferred biomarker for assessing risk of recurrence in the first 5 years after diagnosis, as well as hormonal and chemotherapy responsiveness in HR+ breast cancer patients. RS has been shown to stratify patients into three risk categories (low, intermediate and high), and study data support the recommendation of hormonal therapy alone for patient or hormonal therapy and chemotherapy for patient with low and high RS values, respectively [9, 10, 20]. A meta-analysis including 21 RS studies demonstrated that the mean proportion of patients in the intermediate risk group was 39.4%, with a range from 29.2 to 46.7% [21]. Until recent results from the TAILORx study, for patients classified as intermediate risk, based on their RS value, treatment recommendations were less clear [22].

Previously, we developed and validated the BCI assay consisting of two independently established gene expression biomarkers: Molecular Grade Index (MGI) and HOXB13:IL17BR (H:I) [7, 15]. MGI, a 5-gene predictor that objectively recapitulates tumor grade/proliferation is highly prognostic for early (0–5 years post diagnosis) distant disease recurrence, while H:I is prognostic for both early and late (> 5 years post diagnosis) relapse and is predictive of adjuvant [15] and late extended adjuvant hormonal therapy benefit [23]. A head-to-head (direct) comparison of BCI with RS in the TransATAC (Arimidex, Tamoxifen, Alone or in Combination) cohort revealed that BCI demonstrated superior prognostic performance for early (0–5 years), late (5–10 years), and overall (0–10 years) distant recurrence [24]. For overall 10-year recurrence, BCI, like RS, stratifies patients into three distinct risk groups. However, for early and late recurrence, BCI differs from RS in that it stratifies patients into two rather than three distinct risk groups [24]. Thus, BCI may be advantageous over contemporary gene expression signatures, as the identification of two rather than three distinct risk groups in the early and late time periods potentially eliminates the intermediate risk category that can account for as many as 40% of HR+ patients [21].

In a study examining the cross-stratification between BCI and RS in the TransATAC cohort, BCI significantly reclassified low and intermediate RS group breast cancer patients into different risk categories with significant differences in distant recurrence rates [25]. Furthermore, BCI was shown to provide additional significant prognostic information to the clinical treatment score and RS [25]. Together, these results demonstrated that BCI have increased prognostic accuracy, and could identify a subset of patients who may potentially benefit from additional therapy, such as extended endocrine therapy or adjuvant chemotherapy.

In the current study, we analyzed the correlation between standard clinical and pathological breast cancer parameters with RS and BCI in a multi-institutional cohort of 560 consecutive patients who completed RS testing between 2007 and 2009 as part of their routine care. In addition, we compared the risk stratification of BCI with RS.

Methods

Patients

The authors identified consecutive female breast cancer patients who underwent the 21-gene assay RS (OncotypeDx, Genomic Health Inc.) testing between 2006 and 2008 at Massachusetts General Hospital (Boston, MA), 2006 and 2009 at Jefferson Medical Center (Philadelphia, PA), 2005–2008 at MD Anderson Cancer Center (Houston, TX), 2004–2007 at Brigham and Women's Hospital (Boston, MA), 2004–2008 at Brigham and Women's Faulkner Hospital (Boston, MA), 2005–2007 at Newton-Wellesley Hospital (Newton, MA), and 2005–2008 at North Shore Medical

Center (Salem, MA) as part of their routine clinical care. The test was performed on tumor samples from ER + breast cancer patients who were considering adjuvant chemotherapy. A total of 594 cases were identified from whom sufficient tumor tissue was available for BCI testing (Biotheranostics Inc.). Demographic, pathological, and clinical data were extracted from prospectively maintained clinical databases from each institution. This study was approved by each of the participating institution's review board. At the date of analysis, long term clinical follow up data were not available.

Analytical methods

The RS assay was performed on formalin-fixed paraffin-embedded (FFPE) samples at Genomic Health, Inc. (Redwood City, CA, USA) and RS risk groups were determined as previously described [9, 10]. RNA extraction and assessment of BCI in the study samples was conducted at Biotheranostics, Inc. (San Diego, CA, USA) as previously described [15]; the BCI assay using total RNA extracted from FFPE tumor blocks was performed blinded to all clinical and pathological information. The BCI low-, intermediate-, and high-risk groups were determined using pre-specified cut-points; 5.0825 and 6.5025 [15]. REMARK biomarker criteria are provided as described [26].

Statistical analysis

Comparison of variables between the different risk groups were compared using ANOVA for continuous variables, and Chi square test or Fisher exact test for categorical variables. To assess the correlation between continuous variables, we used the Pearson correlation coefficient. The weighted kappa statistic was used as a measure of concordance between RS and BCI and Bowker's test of symmetry was used to test the concordance between the two prediction tools. Two-tailed significance tests were conducted at a significance level of 0.05. All calculations and statistical tests were performed using the STATA software package version 13.1 (StataCorp LP, College Station, TX).

Results

Patient demographics

A total of 594 FFPE tumor samples were collected and RNA was extracted. Exclusion of samples that failed either of the assays (11 for RS, 2 for BCI), or quality control (8 for BCI) resulted in a total of 573 patients. In the final cohort, only HR+ samples were included, which rendered a total number of 560. Clinicopathological characteristics were extracted from medical records (Tables 1, 2). In brief, the median age

Table 1 Clinical-patholgoical characteristics and risk stratification of estrogen receptor-positive patients by Oncotype Dx Recurrence Score (RS)

Recurrence score (RS) risk groups	Low risk ($n=298$)	Intermediate risk ($n=221$)	High risk ($n=41$)	p value
Age, years (mean ± SD)	54 ± 9	53 ± 9	58 ± 10	0.0035
Tumor size, cm (mean ± SD)	1.6 ± 0.9	1.6 ± 0.9 (4 missing)	1.7 ± 0.8	0.69
Histology (no., %)				
IDC	243 (82)	186 (85)	40 (98)	0.061 (Fisher's exact test)
ILC	34 (11)	24 (11)	0	
Other	21 (7)	10 (5)	1 (2)	
Unknown		1 (0.4)		
Grade (no., %)				
1	75 (25)	46 (21)	4 (10)	< 0.001
2	208 (70)	133 (60)	24 (59)	
3	15 (5)	42 (19)	13 (32)	
HER-2 overexpression (no., %)				
No	296 (100)	218 (99)	30 (75)	< 0.001
Yes	1 (0.3)	3 (1)	10 (25)	
Unknown	1 (0.3)	0	1 (2)	
Lymph node involvement (no., %)				
N_1	8 (3)	13 (6)	1 (2)	0.36 (Fisher's exact)
N_0	278 (93)	204 (92)	40 (98)	
N_{Mic}	7 (2)	3 (1)	0	
Not determined	5 (2)	1 (0.5)	0	

All calculations were performed without the unknowns

Table 2 Clinical-pathological characteristics and risk stratification of estrogen receptor-positive patients by Breast Cancer Index (BCI)

BCI risk groups	Low risk ($n=289$)	Intermediate risk ($n=164$)	High risk ($n=107$)	p value
Age, years (mean ± SD)	53 ± 9	54 ± 9	55 ± 10	0.43
Tumor size, cm (mean ± SD)	1.5 ± 0.9 (3 missing)	1.6 ± 0.8	1.8 ± 1.0 (1 missing)	0.016
Histology (no., %)				
IDC	232 (80)	138 (84)	99 (93)	0.015 (Fisher's exact)
ILC	34 (12)	18 (11)	6 (6)	
Other	23 (8)	8 (5)	1 (0.9)	
Unknown			1 (0.9)	
Grade (no., %)				
1	92 (32)	25 (15)	8 (7)	< 0.001
2	181 (63)	114 (70)	70 (65)	
3	16 (6)	25 (15)	29 (27)	
HER-2 overexpression (no., %)				
No	287 (99)	159 (97)	98 (92)	< 0.001
Yes	1 (0.4)	4 (2)	9 (8)	
Unknown	1 (0.4)	1 (0.6)	0	
Lymph node involvement (no., %)				
N_1	15 (5)	4 (2)	3 (3)	0.015 (Fisher's exact)
N_0	263 (91)	157 (96)	102 (95)	
N_{Mic}	9 (3)	1 (0.6)	0	
Not determined	2 (0.7)	2 (1)	2 (2)	

All calculations were performed without the unknowns

was 54 years (min–max: 27–79 years) and a majority of the tumors were smaller than 2 cm (79%). About two-thirds (65%) were of histologic grade II. In the cohort, 3% of the tumors were HER2 positive, and lymph node involvement was recorded for 4% of the cases.

Association between RS and standard clinical-pathological prognostic parameters

Patients were divided into three risk groups based upon previously defined RS categories. Low-risk, intermediate-risk, and high-risk scores were reported in 298 (53.2%), 221 (39.5%), and 41 (7.3%) patients, respectively (Table 1). High-grade tumors were significantly more prevalent among high-risk RS patients and observed in 31.7% of this group, compared with 5% in the low-risk RS category (Table 1). An overall significant association between grade and RS was observed (Table 1, Kendall's tau-$b=0.1864$, $p<0.00001$). All risk groups displayed a similar distribution of tumor size and no correlation was observed between size and RS (Fig. 1a). The median age of patients in the three RS groups were significantly different ($p=0.035$; Table 1), with higher mean age in the high-risk group (58 years) than in the intermediate and low-risk groups (53 and 54 years, respectively). However, there was not a significant correlation between the continuous RS and age (Fig. 1b). A non-ductal histology was present in 2.5% of the high-risk breast cancer patients, as compared with 18.5% and 15.4% of the low-risk and intermediate-risk RS patients, respectively (Table 1). None of the RS high-risk patients displayed an invasive lobular carcinoma (ILC) histology, but this subtype occurred in 11% in the other two RS groups. The RS assay was performed in 14 HER-2 positive and 22 lymph node positive patients as part of their clinical care. The majority of HER-2 overexpressors were stratified into the high-risk group (10/14), corresponding to 25% of RS high-risk patients, compared with 0.77% of the combined low- and intermediate risk groups ($p<0.001$). The prevalence of lymph node involvement was found to be similar in all RS groups.

Association between BCI and standard clinical-pathological prognostic factors

Based upon previously defined risk categories, BCI stratified 289 (51.6%), 164 (29.3%), and 107 (19.1%) of the patients to the low, intermediate, and high-risk groups, respectively (Table 2). High-grade tumors were significantly more prevalent among high-risk BCI patients; 27.1% of this group, compared with 5.5% in the low-risk BCI category (Table 2). The overall association between grade and BCI was statistically significant (Table 2, Kendall's tau-$b=0.2872$, $p<0.00001$). The association

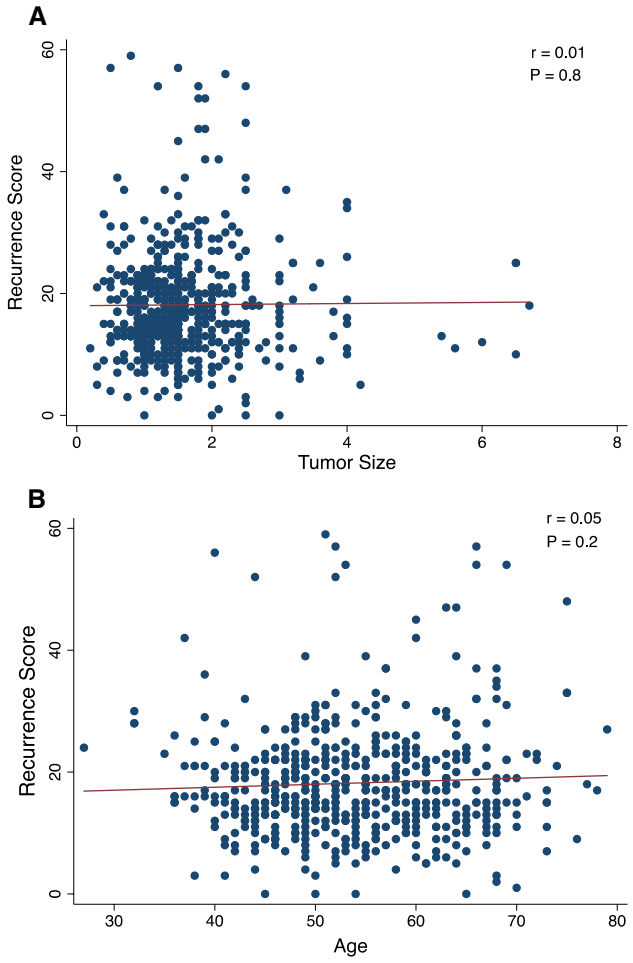

Fig. 1 Correlation between recurrence score and **a** tumor size and **b** age

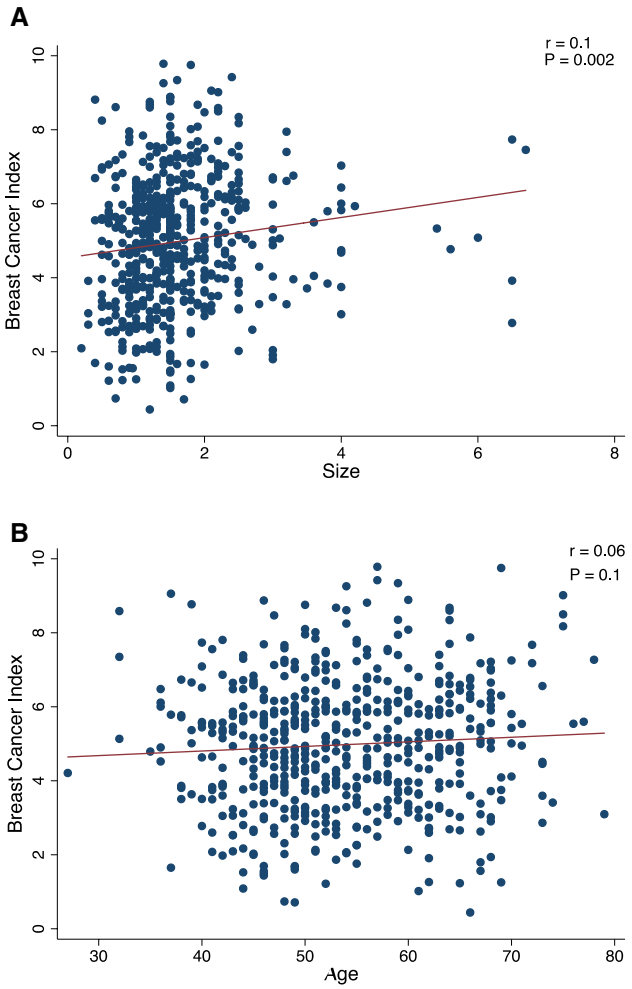

Fig. 2 Correlation between Breast Cancer Index and **a** tumor size and **b** age

between larger tumor size and higher BCI risk category approached significance ($p = 0.066$), and there was a very modest but significant correlation between tumor size and continuous BCI values. However, the absolute size difference between the groups (1.8 cm in high-risk group vs. 1.5 and 1.6 cm in low and intermediate groups, respectively) was of no clinical significance, as the T stage remained unchanged. Similar age distributions were observed in all BCI risk groups and no correlation was detected between age and BCI value (Fig. 2b). The non-ductal histological subtypes of carcinoma were significantly less prevalent among high-risk BCI patients and were observed in 6.6% of this group, compared with 19.7% in the low-risk BCI group. HER-2 overexpression was found to be significantly more prevalent in the high-risk (8.4%) than in the low-risk group (0.35%). Lastly, the prevalence of lymph node involvement did not significantly differ between the risk groups.

Comparison of risk stratification with BCI and RS

Figure 3 shows the correlation between BCI and RS as continuous variable; the moderately strong correlation was statistically significant ($r = 0.4$, $p < 0.001$; Fig. 3). Despite this modest correlation, RS classified notably more women into intermediate risk (39.5% vs. 29.3%), and fewer patients into high risk (7.3% vs. 19.1%). Hence, BCI stratified fewer patients into the intermediate risk group than RS in this clinical series. These differences were statistically significant ($p < 0.001$; Chi square analysis).

A total of 286 of the 560 patients were differentially stratified with the two risk stratification tools, which corresponds to 51.1% of the total ER positive cohort and represents a highly significant discordance (Table 3; $p < 0.0001$ via Bowker's test of symmetry). The concordance between the two risk assessors was 0.240 (weighted kappa; 95% confidence interval 0.172–0.308), which suggests fairly poor agreement. Interestingly, 7.4% of the patients in the RS

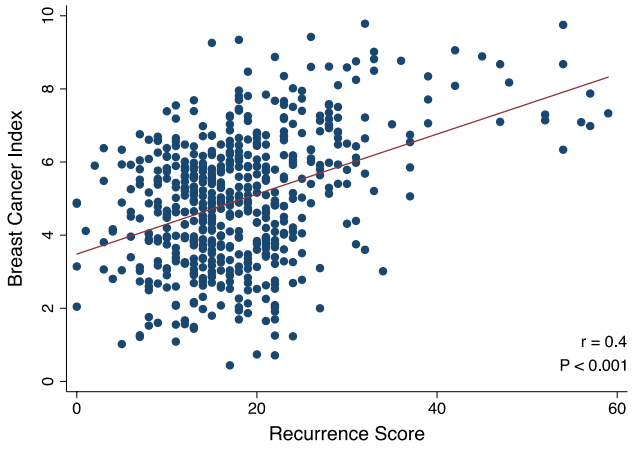

Fig. 3 Correlation between recurrence score and Breast Cancer Index

low-risk group were recategorized into the BCI high-risk group, and, 12% of RS high-risk patients were designated as low risk of recurrence as assessed by BCI. Conversely, 1.7% of BCI low-risk patients were allocated to the RS high-risk category, and 20.1% of the BCI high-risk patients were stratified into the low-risk group according to RS. Among the patients for which the two biomarkers showed discrepancy, we could not find any common clinicopathological characteristics.

Discussion

In the current study, we report on the association between RS and BCI with standard clinical and pathological parameters, and a comparison of categorical risk stratification between BCI and RS in a multi-institutional cohort of 560 early-stage ER+ breast cancer patients who were referred as part of their routine clinical care to undergo OncotypeDx testing. The mean age of the patients referred for RS was 54 years, and the majority of tumors was < 2 cm (79%) and histologic grade II (65%). All but 14 of the tumors were HER2 non-amplified. Overall, these demographics are similar to what previously has been reported for patients referred for clinical RS testing [27–32] and are consistent with the guidelines given by the National Comprehensive Cancer Network (NCCN).

In our study, RS and BCI stratified a similar proportion (53% vs 52%) of patients into the low-risk group, while BCI stratified a larger proportion (19% vs 7%) of patients into the high-risk group. BCI and RS risk groups demonstrate a significant association with histological tumor grade with high and low-grade tumors more prevalent among RS and BCI high- and low risk patients, respectively. These findings are consistent with previous observations [9, 10, 33, 34], We observed no correlation between RS with patient age or tumor size as continuous variables and these results are in line with previous reports [10, 30, 31, 35]. As it relates to BCI, we did not see a difference in the mean age across the risk groups, and no correlation between these two variables was observed. However, in contrast to RS, there was an association between BCI and tumor size, although very modest, but yet statistically significant.

Of all the patients included in the present study, 58 (10%) displayed an ILC phenotype. None of the ILC cases was classified as RS high-risk, and this observation is consistent with previous reports describing a low incidence of ILC cases within the RS high-risk group [33, 36]. On the other hand, 6% of ILC cases were classified as BCI high-risk. Although ILC tumors display features often associated with a good prognosis, these tumors can be highly metastatic [37] and several studies demonstrate that the overall long-term outcome for patients diagnosed with ILC is worse than for patients diagnosed with IDC [38, 39]. We have shown that BCI predicts for late disease recurrence (5–10 years post diagnosis) while RS does not [24, 40]. Thus, the discrepancy in classification of ILC cases into the high-risk category may reflect the difference in prognostic performance of BCI and RS as it relates to late disease recurrence.

In this series of patients, the overall risk-group stratification correlation between RS and BCI was poor, with a weighted kappa of 0.240. In total, 182 (32.5%) women were classified into the low-, 63 (11.3%) into the intermediate-, and 29 (5.2%) into the high-risk groups by both BCI and RS, leading to a concordance of 51% between RS and BCI

Table 3 Cross-stratification of women into respective risk groups by Recurrence Score (RS) and Breast Cancer Index (BCI)

	Recurrence Score			
Breast Cancer Index (BCI)	Low	Intermediate	High	Total
Low	182	102	5	289
Inter	94	63	7	164
High	22	56	29	107
Total	298	221	41	560

Gray shaded area, reclassified into higher risk groups by BCI; blue shaded areas, reclassified into lower risk groups by BCI

risk categories (Table 3). Among the 286 (51%) discordant cases, 46.2% of RS intermediate risk patients were re-stratified into BCI low and 25.3% into BCI high risk groups (Table 3). Notably, these latter findings are in line with the clinical outcome-based results from our previous TransATAC study in which BCI significantly re-stratified 53% and 19% of the RS intermediate risk group into BCI low and high risk groups, respectively [23]. Thus, taken together, our findings may have implications for clinical treatment decision making for women with early-stage breast cancer. For example, our findings suggest that a significant proportion of RS intermediate risk patients are at low risk of recurrence and will benefit from upfront endocrine therapy alone, while a smaller but significant proportion of the RS intermediate risk patients are at an elevated risk of late recurrence and will likely benefit from the addition of extended endocrine therapy. Although the results of the TAILORx clinical trial suggest that the 21-gene RS assay may identify 85% of early stage breast cancer who can be spared chemotherapy, it did not address the identification of those patients who can be spared extended adjuvant endocrine therapy [22].

Strengths of this analysis are the multi-institutional nature of the study and the large sample size of early stage breast cancer patients who underwent RS testing as part of their routine clinical care. An additional strength of this study is that the findings are highly similar to those from our previous comparative analysis of RS and BCI in the TransATAC clinical trial cohort. A notable limitation of this study is the lack of long term clinical follow-up, and thus the inability to definitively confirm our previous observations [23]. However, our results provide additional evidence to support a comparative assessment of the chemotherapy and extended hormonal therapy predictive performance BCI with RS in clinical studies such as TAILORx Breast Cancer Trial (Trial Assigning Individualized Options for Treatment) and NSABP-B42, respectively.

Conclusions

The ability to predict upfront chemotherapy response or extended adjuvant hormonal therapy response for early-stage ER+ breast cancer patients is a pressing question. Herein, we have shown that BCI and RS differentially stratify early-stage ER+ patients. The BCI high-risk group is larger and the intermediate risk group is smaller as compared to the corresponding RS risk groups. Thus, BCI may provide more additional genomic information to better individualize risk assessment for RS intermediate-risk early-stage breast cancer patients.

Author contributions PLJ and NH performed the statistical analysis, contributed to the interpretation of data and helped draft and revise the manuscript. YZ, JB, JP, TW, MM, AG, YW, CS, BS, MGE, and PEG participated in the data collection. DCS was the principal investigator, designed the study, participated in data acquisition, prepared the data, contributed to the interpretation of data and helped to draft and revise the manuscript. All authors have read and approve of the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest Drs. Zhang, Schnabel, and Schroeder disclose that they are employees and shareholders in Biotheranostics, Inc. Drs. Sgroi, Zhang, Erlander, and Schnabel disclose they are named inventors on a patent to use the Breast Cancer Index. *HOXB13/IL7BR*, and Molecular Grade Index assays to predict breast cancer outcomes. Drs Jerevall, Brock, Palazzo, Wieczorek, Misialek, Guidi, Yun, Goss, and Horick have no relevant financial relationships with commercial interests to disclose.

Ethical approval The study conducted complies with the current ethical standard laws of the United States, and was approved by each of the participating institution's review board.

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