Breast Cancer Index re-stratifies 21-gene assay risk groups for risk of recurrence and extended endocrine therapy benefit: Final Analysis of the BCI Registry Study

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Introduction

- Patients face a prolonged risk of late distant recurrence (DR) with HR+ early stage breast cancer, even after 5 years of adjuvant endocrine therapy.
- The BCI Registry is a prospective, multi-institutional study that enrolled > 3000 patients to evaluate the long-term clinical outcome, decision impact, and endocrine therapy adherence.
- The Breast Cancer Index (BCI) is a genomic classifier that:
  - Prognosticates risk of overall (0-10y) and late (post 5 years) distant recurrence (DR)
  - predicts the likelihood of benefit from extended endocrine therapy (EET) based on the H/I (HOXB13/IL-17BR) gene expression ratio.
- The 21-gene Recurrence Score (RS) is a genomic classifier:
  - Prognosticates recurrence risk
  - Predict benefit from adjuvant chemotherapy in HR+/HER2− breast cancer patients
  - The TAILORx trial revealed that chemotherapy is not beneficial for women with HR+/HER2-, node-negative breast cancers with low or intermediate-risk RS.
  - The RxPONDER trial assessed the efficacy of chemotherapy in women with early-stage, HR+, node-positive breast cancer. Most postmenopausal women can safely avoid adjuvant chemotherapy with low RS. Conversely, RS was not predictive of CT benefit in premenopausal women.
- **The objective of this analysis is to investigate the relationship between BCI (H/I) and RS in the BCI Registry study in HR+/HER2- patient cohort.**

Methods

- Based on TAILORx and RxPONDER results, RS stratified patients into four risk groups:
  - age ≤ 50, No CT benefit (RS≤15)
  - age ≤ 50, CT benefit (RS>15)
  - age > 50, No CT benefit (RS≤25)
  - age > 50, CT benefit (RS>25)
- Kendall's correlation coefficient (R) was used to estimate the correlation between the BCI prognostic score, H/I and RS as continuous variables. Cohen's kappa (κ) was used to measure the agreement between H/I and RS categories.

Figure 1: REMARK diagram of available BCI Registry Patients



Results

Table 1: Overall cohort characteristics (N=1238)

	RS risk categories				BCI (H/I) groups	
	Age≤50, No CT benefit N = 45 (3.6%)	Age ≤50, CT benefit N = 54 (4.4%)	Age >50, No CT benefit N = 976 (78.8%)	Age >50, CT benefit N = 163 (13.2%)	BCI (H/I)-Low N = 834 (67.4%)	BCI (H/I)-High N = 404 (32.6%)
Menopausal status						
Perimenopausal	2 (4.4%)	1 (1.9%)	21 (2.2%)	0 (0.0%)	18 (2.2%)	6 (1.5%)
Postmenopausal	14 (31.1%)	15 (27.8%)	900 (92.2%)	157 (96.3%)	717 (86.0%)	369 (91.3%)
Premenopausal	29 (64.5%)	38 (70.3%)	55 (5.6%)	6 (3.7%)	99 (11.8%)	29 (7.2%)
T stage						
T1	31 (68.9%)	41 (75.9%)	752 (77.1%)	113 (69.3%)	640 (76.8%)	297 (73.6%)
T2	14 (31.1%)	11 (20.4%)	209 (21.4%)	50 (30.7%)	182 (21.8%)	102 (25.2%)
T3	0 (0.0%)	2 (3.7%)	15 (1.5%)	0 (0.0%)	12 (1.4%)	5 (1.2%)
Grade						
Well	17 (37.8%)	16 (29.7%)	304 (31.1%)	16 (9.8%)	274 (32.9%)	79 (19.6%)
Moderate	25 (55.5%)	26 (48.1%)	583 (59.8%)	89 (54.6%)	477 (57.1%)	246 (60.8%)
Poor	3 (6.7%)	12 (22.2%)	89 (9.1%)	58 (35.6%)	83 (10.0%)	79 (19.6%)
Histological type						
Ductal	36 (80.0%)	49 (90.7%)	773 (79.2%)	147 (90.2%)	670 (80.3%)	335 (82.9%)
Lobular	6 (13.3%)	2 (3.7%)	172 (17.6%)	13 (8.0%)	135 (16.2%)	58 (14.4%)
Other	3 (6.7%)	3 (5.6%)	31 (3.2%)	3 (1.8%)	29 (3.5%)	11 (2.7%)
Nodal status						
N0	37 (82.2%)	47 (87.0%)	805 (82.5%)	148 (90.8%)	705 (84.5%)	332 (82.2%)
N1	8 (17.8%)	7 (13.0%)	171 (17.5%)	15 (9.2%)	129 (15.5%)	72 (17.8%)
ER status						
Positive	45 (100.0%)	54 (100.0%)	974 (99.8%)	163 (100.0%)	833 (99.9%)	403 (99.8%)
Negative	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	1 (0.1%)	1 (0.2%)
PR status						
Positive	45 (100.0%)	52 (96.3%)	905 (92.7%)	114 (69.9%)	764 (91.6%)	352 (87.1%)
Negative	0 (0.0%)	2 (3.7%)	71 (7.3%)	49 (30.1%)	70 (8.4%)	52 (12.9%)

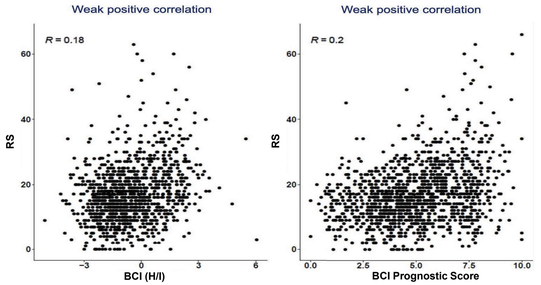
- Patient tumors were 83.8% N0, 75.7% T1 and 58.4% moderate grade, 87.7% postmenopausal

Table 2. Clinical characteristics of Low risk RS (0-11) and BCI High risk/ (H/I) High (N=52)

	Age≤50, N = 3 (0.24%)	Age >50, N = 49 (3.77%)	RS=0, N = 2 (0.16%)
Menopausal status			
Perimenopausal	0 (0.0%)	2 (4.1%)	0 (0.0%)
Postmenopausal	1 (33.3%)	44 (89.8%)	2 (100.0%)
Premenopausal	2 (66.7%)	3 (6.1%)	0 (0.0%)
Tumor stage			
T1	1 (33.3%)	35 (71.5%)	2 (100.0%)
T2	2 (66.7%)	13 (26.5%)	0 (0.0%)
T3	0 (0.0%)	1 (2.0%)	0 (0.0%)
Tumor Grade			
Well	0 (0.0%)	5 (10.2%)	1 (50.0%)
Moderate	2 (66.7%)	37 (75.5%)	1 (50.0%)
Poor	1 (33.3%)	7 (14.3%)	0 (0.0%)
Nodal status			
N0	2 (66.7%)	37 (75.5%)	2 (100.0%)
N1	1 (33.3%)	12 (24.5%)	0 (0.0%)
Histological type			
Ductal	1 (33.3%)	37 (75.5%)	1 (50.0%)
Lobular	1 (33.3%)	10 (20.4%)	0 (0.0%)
Other	1 (33.3%)	2 (4.1%)	1 (50.0%)
BCI Score median(Range)			
	5.5 (5.3-8.8)	6.7 (5.1-10.0)	5.2 (5.1-5.3)

- 347 out of 1238 patients had a RS of 0-11
- 52 of those patients were BCI High Risk and BCI (H/I)-High
- 2 patients with an RS of 0 were re-stratified as High risk and High likelihood to benefit from EET by BCI

Figure 2: Correlation between BCI (H/I), BCI Prognostic and RS



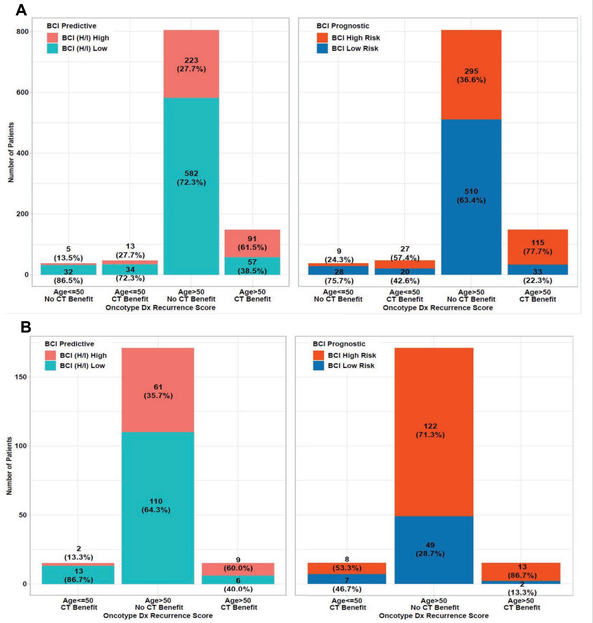
- BCI (H/I) and BCI Prognostic Score showed a weak correlation with RS with R=0.2 and R=0.18, respectively

Table 3: Oncotype DX stratified by BCI Prognostic and BCI Predictive

	All Patients (N=1238)	RS risk categories: Age≤50, No CT benefit (N=45)	Age≤50, CT benefit (N=54)	Age>50, No CT benefit (N=976)	Age>50, CT benefit (N=163)
BCI Prognostic					
Low risk	649 (52.4%)	32 (71.1%)	23 (42.6%)	559 (57.3%)	35 (21.5%)
High risk	589 (47.6%)	13 (28.9%)	31 (57.4%)	417 (42.7%)	128 (78.5%)
BCI Predictive (H/I)					
Low likelihood	834 (67.4%)	38 (84.4%)	41 (75.9%)	692 (70.9%)	63 (38.7%)
High likelihood	404 (32.6%)	7 (15.6%)	13 (24.1%)	284 (29.1%)	100 (61.3%)
BCI Prognostic and BCI Predictive					
Low risk/Low likelihood	547 (44.2%)	29 (64.4%)	21 (38.9%)	475 (48.7%)	22 (13.5%)
Low risk/High likelihood	102 (8.2%)	3 (6.7%)	2 (3.7%)	84 (8.6%)	13 (8.0%)
High risk/Low likelihood	287 (23.2%)	9 (20.0%)	20 (37.0%)	217 (22.2%)	41 (25.2%)
High risk/High likelihood	302 (24.4%)	4 (8.9%)	11 (20.4%)	200 (20.5%)	87 (53.4%)

- BCI stratified 649 patients (52.4%) as low-risk and 589 (47.8%) as high-risk for late DR. RS classified 45 patients (3.6%) as Age ≤ 50, No CT benefit; 54 (4.4%) as Age ≤ 50, CT benefit; 976 (78.8%) as Age > 50, No CT benefit; and 163 (13.2%) as Age > 50, CT benefit
- Among those older than Age 50, the H/I ratio identified 29.1% of those with no predicted CT benefit as likely to benefit from EET
- In comparison, 38.7% of those with predicted CT benefit as not likely to benefit from EET

Figure 3. BCI (H/I) and BCI Prognostic stratified by RS risk categories. A) N0 cohort, TAILORx categories B) N1 cohort, RxPONDER categories



Conclusions

- BCI (H/I) and RS were weakly correlated (R=0.18); BCI Prognostic and RS showed low correlation (R=0.20)
- Based on categorical groups, BCI (H/I) had very low concordance with RS for younger women (Age ≤ 50, Cohen's kappa=0.08, p=0.29) but showed some weak correlation with RS for older women (Age > 50, Cohen's kappa=0.21, p<0.001)
- BCI (H/I) consistently stratified RS risk categories into separate BCI (H/I)-Low and BCI (H/I)-High groups; BCI Prognostic stratified RS risk categories into BCI Low Risk and BCI High Risk groups
- These results confirm that the **21-gene assay should not be used to predict the likelihood of benefit from EET**

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References

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