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CLINICAL TRIAL

Prospective assessment of the decision-making impact of the Breast Cancer Index in recommending extended adjuvant endocrine therapy for patients with early-stage ER-positive breast cancer

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Abstract Extended adjuvant endocrine therapy (10 vs. 5 years) trials have demonstrated improved outcomes in early-stage estrogen receptor (ER)-positive breast cancer; however, the absolute benefit is modest, and toxicity and tolerability challenges remain. Predictive and prognostic information from genomic analysis may help inform this clinical decision. The purpose of this study was to assess the impact of the Breast Cancer Index (BCI) on physician recommendations for extended endocrine therapy and on patient anxiety and decision conflict. Patients with stage I–III, ER-positive breast cancer who completed at least 3.5 years of adjuvant endocrine therapy were offered participation. Genomic classification with BCI was performed on archived tumor tissues and the results were reported to the treating physician who discussed results with the patient. Patients and physicians completed pre- and post-test questionnaires regarding preferences for extended endocrine therapy. Patients also completed the validated traditional Decisional Conflict Scale (DCS) and State Trait Anxiety Inventory forms (STAI-Y1) pre- and post-test. 96 patients were enrolled at the Yale Cancer Center [median age 60.5 years (range 45–87), 79 % postmenopausal, 60 % stage I). BCI predicted a low risk of late recurrence in 59 % of patients versus intermediate/high in 24 and 17 %,

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respectively. Physician recommendations for extended endocrine therapy changed for 26 % of patients after considering BCI results, with a net decrease in recommendations for extended endocrine therapy from 74 to 54 %. After testing, fewer patients wanted to continue extended therapy and decision conflict and anxiety also decreased. Mean STAI and DCS scores were 31.3 versus 29.1 ($p = 0.031$) and 20.9 versus 10.8 ($p < 0.001$) pre- and post-test, respectively. Incorporation of BCI into risk/benefit discussions regarding extended endocrine therapy resulted in changes in treatment recommendations and improved patient satisfaction.

Keywords Hormone therapy · Late recurrence · Survivorship · Risk assessment · Anxiety · Satisfaction

Abbreviations

ER	Estrogen receptor
BCI	Breast Cancer Index
DCS	Decisional conflict scale
STAI	State Trait Anxiety Inventory
ROR	PAM50 risk of recurrence
H/I	HoxB13/IL17BR ratio
PR	Progesterone receptor
HIC	Human Investigations Committee
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
FFPE	Formalin-fixed paraffin-embedded tissue

Introduction

The risk of recurrence for many estrogen receptor (ER) positive breast cancers extends over a prolonged period of time and around 50 % of all recurrences develop after the first 5 years of follow-up ("late recurrence") [1]. Importantly, extended adjuvant endocrine therapy can reduce the risk of late recurrences. In 5 different randomized controlled trials (NCIC-CTG MA.17, NSABP-B33, ABCSG-6a, ATLAS, and aTTom), which investigated either aromatase inhibitors following an initial 5 years of tamoxifen [2–6] or 10 years of tamoxifen versus 5 years [7, 8], extended endocrine therapy reduced the risk of late disease recurrence. While these studies have established that extended endocrine therapy is superior to 5 years of adjuvant endocrine treatment; they also demonstrated that the absolute benefit from prolonged endocrine therapy is modest (approximately 3–5 % absolute benefit across studies) and comes with added toxicity. For example, in the ATLAS trial, 10 years of tamoxifen resulted in increased risk for pulmonary embolism (RR 1.87, 95 % CI

1.13–3.07, $p = 0.01$) and endometrial cancer (RR 1.74, 95 % CI 1.30–2.34, $p = 0.0002$) [7]. The cumulative risk of endometrial cancer during years 5–14 was 3.1 % for 10 years of tamoxifen compared to 1.6 % for 5 years [7, 9]. Extended adjuvant therapy with aromatase inhibitors after tamoxifen also causes an increase in the risk for osteoporosis, which may lead to unfavorable serum lipid profiles, and is associated with arthralgias and menopause side effects [4, 10]. In the MA17 trial, osteoporosis incidence was 8.1 % in the letrozole group compared to 6 % in controls ($p = 0.003$). Hot flashes, anorexia, arthralgia, myalgia were also statistically significantly more common in the letrozole arm [4]. Because of the modest efficacy, potential for adverse events, and costs of therapy, there is an unmet need for tools to help identify women who are at risk for late recurrence and have endocrine sensitive cancers and therefore would benefit the most from prolonged endocrine therapy [11, 12].

Clinical variable-based risk prediction models such as Adjuvant! Online predict cumulative risk of recurrence over a 10-year period but do not distinguish between risks for early versus late relapse [13]. Furthermore, analyses from the extended endocrine therapy clinical trials have shown that clinicopathologic factors, including tumor size, grade, nodal status, and quantitative ER are not predictive for benefit from endocrine therapy [4, 6, 7, 14]. Recent studies suggested that the 21-gene recurrence score (RS) is most accurate to assess risk of recurrence in the first 5 years and is less useful to predict late recurrences [15–18]. Several emerging molecular diagnostic assays including the EndoPredict test, the PAM50 risk of recurrence (ROR) score, and the Breast Cancer Index (BCI) tests have demonstrated the ability to specifically assess risk of late recurrence in ER-positive cancers [14, 19–22]. BCI is an 11-gene, gene-expression-based assay that incorporates both a proliferation component and an estrogen signaling component [19]. In addition to being validated in 2 randomized trial cohorts as a prognostic tool for risk of late recurrence, BCI also incorporates an endocrine response biomarker (HoxB13/IL17BR ratio [H/I]), which has been demonstrated in 3 randomized controlled trial cohorts to predict benefit from endocrine therapy [14, 19, 23]. BCI reports prognostic risk separately for early and late recurrence and also provides the likelihood of benefit from extended endocrine therapy based on the H/I ratio. While the test has been clinically validated, to-date, there have not been studies to examine the clinical utility of the test on treatment recommendations for extended endocrine therapy. The primary objective of this study was to prospectively assess the impact of the BCI results on physicians' recommendation for extended adjuvant endocrine therapy and to assess its effect on patient decision conflict, anxiety, and satisfaction with the treatment recommendation.

Methods

This study was approved by the Human Investigations Committee (HIC) and all participants signed informed consent.

Patients

All women with a history of ER or progesterone receptor (PR) positive, stage I–III breast cancer, who have completed at least 3.5 years of adjuvant endocrine therapy and were eligible for further extended adjuvant endocrine therapy were offered participation in the study. The research assistant identified eligible patients who were coming to the breast cancer clinic for routine follow-up. The research assistant alerted the treating physicians who then discussed the study with the patient. Both the patient and her treating physician had to agree to complete a pretest and a post-test questionnaire (Supplementary appendix). Patient information including demographic data, comorbid illnesses, breast cancer characteristics (TNM stage, histologic grade, ER, PR, and HER status) and treatment history including side effects from prior endocrine therapy was collected. Physicians were asked to estimate the patient's risk of recurrence, provide recommendation for extended endocrine therapy, and indicate confidence in the recommendation before testing and after BCI test results became available. Patients reported their perceived risk of recurrence, preference for extended adjuvant therapy and completed the State Trait Anxiety Index (STAI) and the traditional decision conflict scale (DCS) instruments before and after testing (Supplementary appendix). The STAI captures both transient anxiety (state anxiety) and more long-standing anxiety (trait anxiety) [24]. Participants in this study were asked to complete the state anxiety (STAI-Y1) form only as trait anxiety is not expected to be modifiable based on the knowledge of the BCI results. The STAI-Y1 questionnaire includes 20 items which are answered on a 1–4 scale, and the STAI-Y1 score ranges from 20 to 80, with higher score correlating with greater anxiety [24]. The DCS includes 16 statements and 5 Likert-scale response categories that measure personal perceptions of uncertainty when choosing between options. The score ranges from 0 to 100 and higher scores indicate higher decisional conflict and greater difficulty in making a decision [25]. Patients were also queried for concerns of cost, side effects, safety and benefit, level of comfort with the choice of extended therapy before and after the BCI results, and impact on compliance. The median time between completion of the pre- and post-test surveys was 92.5 days (range 21–364).

Molecular testing

BCI is an 11-gene, gene-expression-based (qRT-PCR) assay performed on formalin-fixed paraffin-embedded (FFPE) tissue (BioTheranostics; San Diego, CA). The BCI assay yields a composite score indicating an individualized percentage risk of late distant recurrence (post-5 years) and a categorical (high vs. low) likelihood of benefit from extended endocrine therapy. The assay represents the combination of two distinct predictors [19]. The first is a two-gene endocrine treatment sensitivity marker based on the ratio of HOXB13 and IL17BR expression (H/I) [26, 27], the second is a proliferation marker represented by the average expression of five cell cycle-associated genes BUB1B, CENPA, NEK2, RACGAP1, and RRM2 [27]. The two markers together comprise a proprietary score that ranges from 0 to 10, which is associated with an individualized risk of late recurrence, and is categorized into low (BCI score < 5.1), intermediate ($5.1 \leq$ BCI score < 6.5), and high-risk (BCI score $\geq$ 6.5) groups using previously validated cut-points (note: the intermediate and high-risk groups have similar risk of late recurrence in validation studies) [19]. The BCI report includes 2 distinct elements: an individualized risk of late (5–10 years) distant recurrence and a prediction of likelihood of benefit from extended endocrine therapy based on the H/I biomarker. While the assay provides an individualized assessment of risk between years 5–10, data from one validation study did show significant prognostic ability to year 15 post-diagnosis [19]. The BCI test was performed on archived tumor tissues (primary tumor core biopsy or resection specimen) and results were reported to the treating physician who discussed results with the patient.

Statistical considerations

No prior data exist that describe the impact of the BCI results on physician decision-making, therefore, we assumed a recommendation change rate of 25 % (i.e., change from pre-test recommendation of no extended therapy to post-test recommendation of extended therapy or vice versa) which is similar to change rates observed with Oncotype Dx. [28] The study was designed with a sample size of 100 patients to allow estimation of this change rate within an exact binomial 95 % confidence interval half-width of 9 %. Data on physicians' confidence and patients' comfort level regarding the treatment recommendation before and after BCI testing were compared using McNemar's test for paired data; odds ratios (OR) were estimated by conditional logistic regression. The pre- and post-test average DCS and STAI scores were compared using a paired *t* test.

Results

Patient and tumor characteristics

Between February and August 2014, 153 consecutive patients with history of ER-positive, stage I–III breast cancer currently receiving adjuvant endocrine therapy for at least 3.5 years were screened for eligibility at the Breast Center of Yale Cancer Center. Ninety-six patients met all eligibility criteria, agreed to participate in the study, and had sufficient tissue for testing. All 96 patients completed both the pre-and post-test surveys. Figure 1 shows the CONSORT diagram and Table 1 presents the patient characteristics. The median age was 60.5 years (range 45–87), 70 patients had node negative disease, 58 had stage I disease, and 49 patients received adjuvant or neoadjuvant chemotherapy. Thirty patients were receiving adjuvant tamoxifen and the rest an aromatase inhibitor when they entered the study. Thirty patients had normal bone density, and 49 had osteopenia on their most recent bone density measurements within a year of study entry.

Summary of BCI test results

BCI categorized 57 patients as low risk, 23 as intermediate risk, and 16 as high risk for late distant recurrence, while 56 and 40 patients were predicted to have low likelihood and high likelihood of benefit from extended endocrine therapy, respectively. The combinations of prognostic and predictive categorizations are shown in supplementary Table 1. In 43 cases, the assay predicted low risk of late recurrence and a low likelihood of benefit from extended endocrine therapy, while in 26 cases, the assay predicted a high or intermediate risk of late recurrence and high likelihood of benefit from extended endocrine therapy. In 13 cases, patients had high or intermediate prognostic risk, but no predicted benefit from extended endocrine therapy (Supplementary Table 1).

Impact of BCI results on physician decision-making

Prior to the BCI test results, treating medical oncologists assessed 49 % of patients to be low risk for recurrence (defined as less than 5 % risk of recurrence after 5 years of endocrine therapy). An additional 38 % were considered as intermediate risk (i.e., predicted risk of recurrence 6–15 %) and the remaining 13 % as high risk based on physician's judgment. The distribution of subjective risk estimates by physicians with corresponding BCI results are shown in Table 2. Prior to BCI testing, physicians recommended extended endocrine therapy to the majority of patients (71 of 96 patients, 74 %) (Fig. 2). When extended endocrine therapy was not recommended, the main reason was perceived low risk of recurrence (n = 22) followed by risk of osteoporosis (n = 4) and side effects from therapy (n = 3).

Following BCI testing, physicians changed treatment decisions for 25 patients (26 %), Extended adjuvant therapy was recommended to 52 (54 %) of patients, a statistically significant reduction (OR = 0.14; 95 % CI 0.04–0.46; $p = 0.0003$; Fig. 2). The majority of the changes were in patients with low risk of late recurrence and low likelihood of benefit. Changes in physician confidence
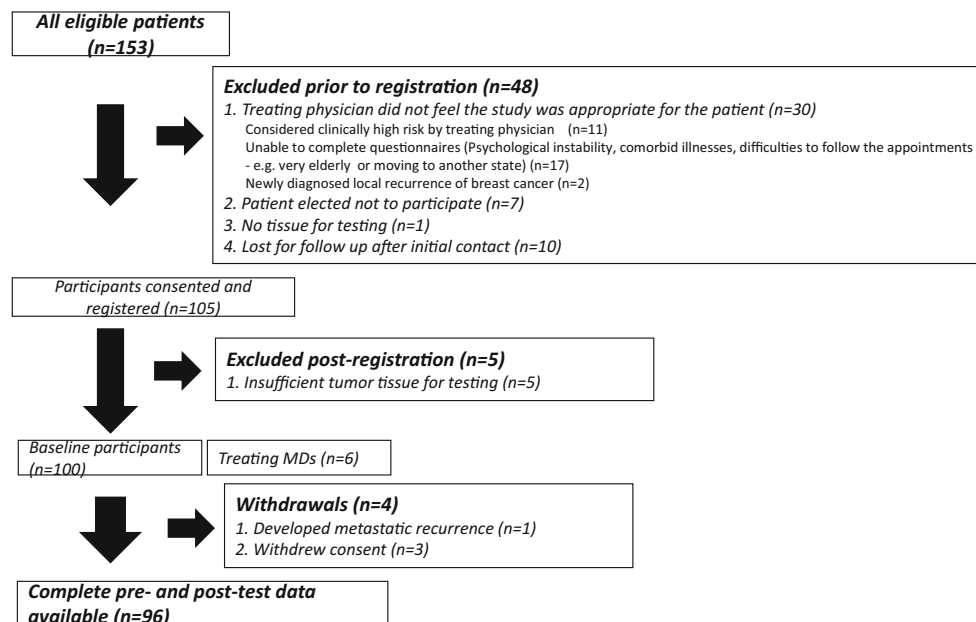
Fig. 1 Consort diagram of the participants

Table 1 Patient and tumor characteristics

Patient and tumor characteristics	(n = 96)	%
Median age (min–max)	60.5 (45–87)	
<50 years old	11	12
≥50 years old	85	88
Caucasian	87	91
African American	5	5
Asian	2	2
Not available	2	2
Premenopausal	13	14
Postmenopausal	76	79
Perimenopausal	7	7
Receptor status		
ER positive	96	100
ER negative	0	
PR positive	85	88
PR Negative	11	12
HER2 positive	9	9
HER2 negative	86	90
HER2 not available	1	1
Histologic grade		
Grade 1	30	31
Grade 2	50	52
Grade 3	16	17
TNM stage (AJCC)		
Stage I	58	60
Stage II	33	35
Stage III	5	5
Tumor size at diagnosis		
T1 (≤2 cm)	65	68
T2 (>2–5 cm)	32	33
T3 (>5 cm)	3	3
T4 (skin involvement)	0	
Nodal status at diagnosis		
N0 (no nodal involvement)	70	73
N1 (1–3 nodes)	22	23
N2 (4–9 nodes)	4	4
N3 (>9 or IC)	0	
Chemotherapy		
Adjuvant	38	40
Neoadjuvant	11	11
None	47	49
Adjuvant endocrine therapy		
Tamoxifen	30	31
Aromatase Inhibitors	66	69
Letrozole	48	50
Anastrozole	16	17
Exemestane	2	2
Last bone density		
Normal	30	31

Table 1 continued

Patient and tumor characteristics	(n = 96)	%
Osteopenia	49	51
Osteoporosis	5	5
Not available	12	13

n number of the patients, *ER* estrogen receptor *PR* progesterone receptor *HER2* human epidermal growth factor receptor 2

are shown in Fig. 3. More physicians felt strongly confident in their recommendation after the test result (24 %) than before (8 %) (OR = 4.75; 95 % CI 1.62–13.96; $p = 0.0035$) (Fig. 3).

## Impact of BCI results on patient treatment decisions, anxiety, and decision conflict

Table 2 shows how the BCI results were distributed across the patient self-reported risk categories. When patients were asked about their perceived risk of recurrence before the test results were presented to them, 25 % indicated that their disease was not likely to come back and 74 % felt that it was somewhat likely that it could come back (Table 2). Moreover, after BCI results were discussed with patients, 50 % felt that their disease was not likely to come back, which represents a significant increase (OR = 9.0; 95 % CI 2.73–29.67; $p < 0.0001$), whereas a significantly reduced number of patients (43 %) thought it was somewhat likely that it could come back (OR = 0.091; 95 % CI 0.028–0.296; $p < 0.0001$). Six patients changed their risk perception to high risk. Following discussion of BCI test results with their physicians, 29 % fewer patients intended to pursue extended endocrine therapy (58 vs. 82; OR = 0.077; 95 % CI 0.018–0.324; $p < 0.0001$) and significantly more patients felt strongly comfortable with their decision (51 vs. 26; OR = 3.78; 95 % CI 1.81–7.88; $p = 0.0003$; Fig. 3).

Mean STAI scores decreased from 31.3 before BCI testing to 29.1 following testing, a significant reduction in overall anxiety level (paired *t* test p-value = 0.031). At the individual patient level, anxiety level decreased in 54 patients, remained stable in 12 patients, and increased in 30 patients (Fig. 4). Mean DCS scores also improved following BCI testing (20.9 to 10.8; paired *t* test $p < 0.001$). At the individual patient level, decision conflict decreased in 62 patients, remained stable in 18 patients, and increased in 16 patients (Fig. 4; supplementary Table 2). Sixty-nine percent of patients reported that knowing BCI test results made them more likely to be compliant with extended endocrine therapy.

Table 2 Subjective risk estimates of patients and physicians versus the Breast Cancer Index (BCI) risk prediction results

| Pre-test recurrence risk perception (risk of relapse after 5 years of endocrine treatment)	Number of patients (% total)	Patients in Breast Cancer Index (BCI) risk groups (% in risk category)		
		Low risk	Intermediate risk	High risk
By physicians				
Low risk (0–5 %)	47 (49)	35 (75)	10 (31)	2 (4)
Intermediate (6–15 %)	37 (38)	18 (49)	9 (24)	10 (27)
High (>15 %)	12 (13)	4 (33)	4 (33)	4 (34)
Total	96 (100)	57 (59)	23 (24)	16 (17)
By patients				
Not at all likely	24 (25)	17 (71)	5 (21)	2 (8)
Somewhat likely	71 (74)	39 (55)	18 (25)	14 (20)
Very likely	1 (1)	1 (100)	0	0
Total	96 (100)	57 (59)	23 (24)	16 (17)

Fig. 2 Medical oncologists' pre- and post-test recommendation for extended adjuvant endocrine treatment
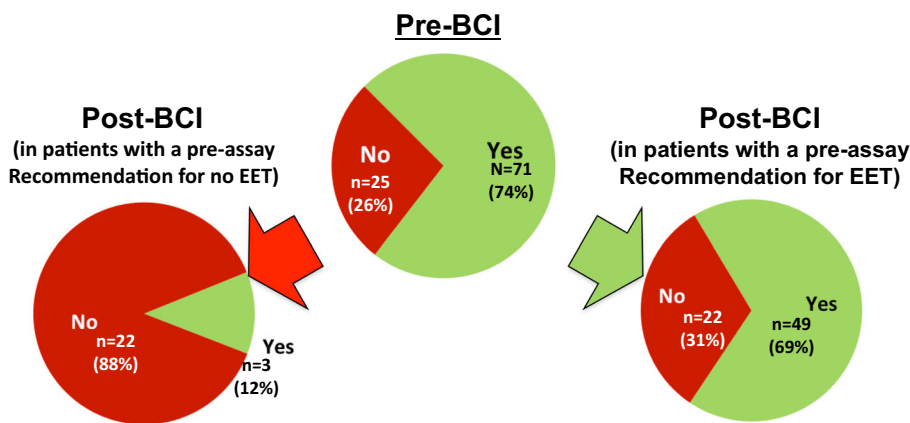
Fig. 3 Medical oncologists' pre-test and post-test level of confidence in treatment recommendation stratified based on whether extended endocrine treatment was recommended in the pre-test and post-test setting (**a**). Patients' pre-test and post-test levels of comfort with the decision for extended adjuvant endocrine treatment stratified based on whether patients preferred extended endocrine treatment in the pre-test and post-test setting (**b**)
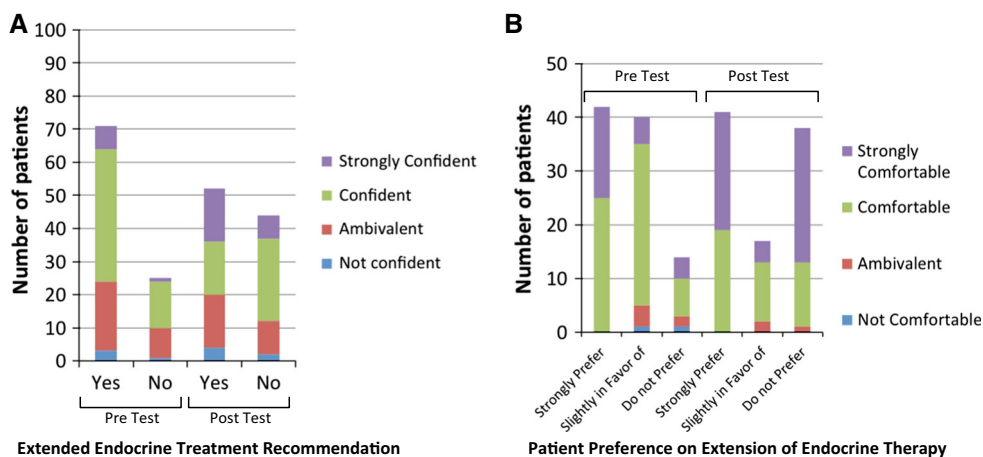
Fig. 4 STAI (**a**) and DCS (**b**) scores for individual patients *before* and *after* BCI assay. Each line connects the pre- and post-test STAI and DCS scores for an individual (*n* = 96 patients). Increasing values post-test are shown in *blue* and decreasing values are shown in *red*. *n* number of the patients, *STAI* state trait anxiety index, *DCS* decision conflict scale, *BCI* Breast Cancer Index
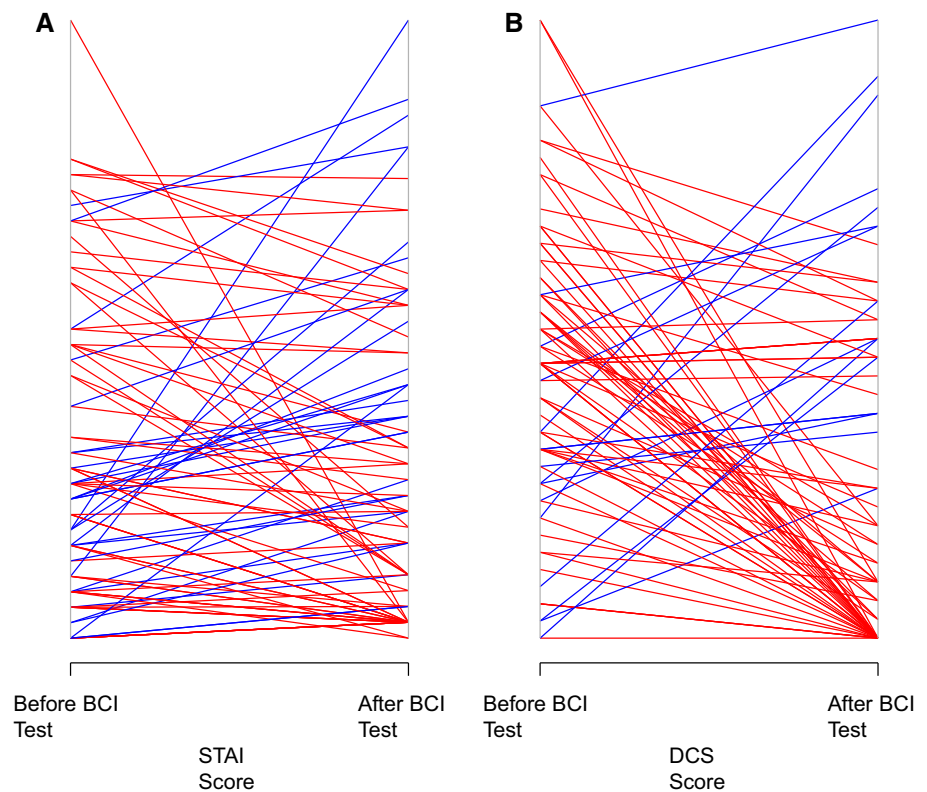
Discussion

This is the first study to prospectively assess the decision-making impact of BCI assay in a routine clinical practice setting in patients who face the decision to continue with extended adjuvant endocrine therapy or stop at 5 years. The results indicate that the test results had a significant effect on both physician treatment recommendation and patient satisfaction. Overall, knowledge of the BCI result led to fewer recommendations for extended endocrine therapy and improved patient satisfaction, and reduced anxiety and decision conflict. We noted that the physicians default tendency was to recommend extended endocrine therapy, consistent with ASCO guidelines and randomized clinical trial results, and patients also favored longer duration of therapy (presumably preferring to err on the cautionary side with potential to reduce the risk of cancer recurrence). This observation is consistent with a recent report that also found that 64 % of physicians recommended extended adjuvant endocrine therapy for eligible patient and 85 % of patients have accepted the recommended treatment [29]. The study results suggest that these choices may be largely based on inflated risk perception. Before testing, 75 % of patients thought that their cancer is very likely or somewhat likely to recur compared to 50 % after the test results became available. Physician estimation of risk of late recurrence was also frequently discordant

with the molecular risk assessment result. Prior to knowing the BCI test results, physicians estimated a high risk of recurrence (>16 %) in 12 patients (13 %). Of these patients, the BCI test was high risk in 33 %, intermediate in 33 %, and low in 33 %. In two cases, the low-risk category results lead to recommendations to forgo extended endocrine therapy. Conversely, 49 % of those estimated by physicians to have an intermediate (6–15 %) risk of recurrence had a low risk BCI. The net effect of testing was a decreased perception of risk of late recurrence and reduced recommendation rate for extended endocrine therapy. As expected, when a therapeutic decision is supported by a test result that is perceived as objective, the comfort level with the treatment recommendation increases for both physicians and patients. However, when the clinical risk estimate and molecular risk estimate are widely discordant, this could increase anxiety and ambivalence, which we also observed in a minority of cases.

The results of this study are relevant within the context of the evolving standard of chronic care for patients with early-stage ER-positive breast cancer. Following the completion of the landmark extended adjuvant endocrine therapy trials, more patients are being recommended for 10 years of adjuvant endocrine therapy; however, without patient selection, the number-needed-to-treat is high. Assessment of risk vs benefit, particularly for patients with favorable prognostic features [11], must balance the

likelihood of benefit from extended therapy against the potential for serious toxicities, tolerability, and quality of life considerations. The findings herein suggest that integrating validated genomic information to help stratify patients based on individualized risk of late recurrence and likelihood of benefit from extended endocrine therapy impacted risk vs benefit discussions and treatment recommendations. Finally, these results may have implications in the context of survivorship program initiatives [30], as a greater proportion of patients reported strong comfort with their treatment decisions as well as reductions in patient anxiety and decision conflict.

This study has several limitations. First, we did not regulate the nature of information exchange between physicians and patients, but recognize that how the test results were communicated could have impacted patient perception about its value. This limitation can also be perceived as a practical strength since the results reflect the outcome of typical patient–physician interactions as they take place in the clinic. This study does not address the prognostic and predictive accuracy of the BCI test, which has been published in a series of peer-reviewed manuscripts previously [14, 19, 20]. The patient population was mostly Caucasian and from an academic medical center which may limit the generalizability of the results.

In summary, extended endocrine therapy decision-making has been challenging, given the high number of patients needed to treat in order to obtain benefit and the well-established safety and tolerability challenges with endocrine therapies [11]. Incorporation of BCI assay testing led to altered medical recommendation in 26 % of cases, fewer recommendations for extended endocrine therapy, and improved patient satisfaction.

Compliance with ethical standards

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