Health Economic Analysis of Breast Cancer Index in Patients With ER+, LN– Breast Cancer

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ABSTRACT

Objectives

Breast Cancer Index (BCI) is a novel gene expression-based test for patients with estrogen receptor positive (ER+), lymph node negative (LN–) breast cancer that predicts risk of recurrence over 10 years, and also specifically predicts risk of late (≥5 y) recurrences and likelihood of benefit from extended (≥5 y) endocrine therapy. The objective of this study was to evaluate cost utility of BCI from a US third-party payer perspective.

Study Design

Two fact-based economic models were developed to project the cost and effectiveness of BCI in a hypothetical population of patients with ER+, LN– breast cancer compared with standard clinicopathologic diagnostic modalities.

Methods

Costs associated with adjuvant chemotherapy, toxicity, follow-up, endocrine therapy, and recurrence were modeled over 10 years. The models examined cost utility compared with standard practice when used at diagnosis and in patients disease-free at 5 years post diagnosis.

Results

Use of BCI was projected to be cost saving in both models. In the newly diagnosed population, net cost savings were $3803 per patient tested. In the 5 years post diagnosis population, BCI was projected to yield a net cost savings of $1803 per patient tested. Sensitivity analyses demonstrated that BCI was cost saving across a wide range of clinically relevant input assumptions.

Conclusions

BCI was projected to be cost saving when used either at diagnosis or at 5 years post diagnosis. Cost savings are achieved through projected impact on adjuvant chemotherapy use, extended endocrine therapy use, and endocrine therapy compliance. These findings require validation in additional cohorts, including studies of real-world clinical practice.

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Each year more than 230,000 women are diagnosed with breast cancer in the United States.[1] The clinical subset of patients with estrogen receptor positive (ER+), lymph node negative (LN–) breast cancer has a better overall prognosis than patients in other clinical subsets (eg, triple negative breast cancer, human epidermal growth factor receptor 2–positive [HER2+] breast cancer). However, one of the hallmarks of ER+ breast cancer is the persistent risk of recurrence that extends greater than 15 years after initial diagnosis and treatment.[2] In addition to surgical intervention and 5 years of endocrine-based therapy, patients and physicians have 2 important therapeutic considerations: first, whether or not to receive adjuvant chemotherapy; and second, whether to extend endocrine-based therapy beyond 5 years. These difficult clinical decisions, which are multifactorial and must balance the potential risks and benefits of therapy, have led to the development of multiple prognostic and predictive tools to assist with clinical decision making.

Significant focus has been placed on supporting the adjuvant chemotherapy decision. Over the past decade, a number of molecular assays designed to predict risk of recurrence and chemotherapy benefit for ER+ patients have become commercially available. These molecular assays have been incorporated into clinical practice, have been shown to impact clinical decision making regarding the use of adjuvant chemotherapy,[3-5] and have been incorporated into clinical guidelines.[6,7] Finally, gene expression–based assays have been shown to be cost saving, through more appropriate patient stratification and utilization of adjuvant chemotherapy.

While significant progress has been made in the area of adjuvant chemotherapy guidance, little progress had been made, until recently, in assessing risk of late (post 5-year) recurrence and in determining the duration of endocrine therapy patients would receive. Focus on this area has grown, given the results of several randomized, prospective clinical trials (eg, MA.17, ATLAS, aTTom) demonstrating clinical benefit of extend-

ing endocrine-based therapy beyond 5 years.[8-11] While statistically significant clinical benefit was observed in all 3 trials, the absolute benefits were relatively small (approximately 3%-6%); this suggests the need, so far unaddressed, to stratify patients based on risk of late recurrence and likelihood of benefit from extended endocrine therapy.

Take-Away Points

This health economic analysis demonstrated that use of Breast Cancer Index in patients with estrogen receptor positive, lymph node negative early breast cancer is cost saving compared with standard management.

- From a third-party payer perspective, use of this test may result in substantially lower overall medical costs.
- The test resulted in cost savings when used either at diagnosis or at 5 years post diagnosis.
- Cost savings were driven by a reduction in adjuvant chemotherapy in patients unlikely to derive benefit (when used at diagnosis), and optimization of extended endocrine therapy utilization in patients likely to receive substantial benefit (when used at either time point).

Breast Cancer Index (BCI; bioTheranostics, San Diego, California) is a gene expression-based biomarker with a novel mechanism of action. BCI was developed through the algorithmic combination of 2 complementary biomarkers: molecular grade index (MGI), which recapitulates tumor grade/proliferation status; and HOXB13:IL17BR ratio [BCI (H/I)], which interrogates estrogen-signaling pathways. In clinical validation studies, BCI has been demonstrated to significantly predict overall (10-year) risk of recurrence, and also specifically predict risk of early (0- to 5-year) and late (≥5-year) recurrence in ER+, LN– breast cancer patients.[12,13] In addition, in a prospective-retrospective analysis of the randomized MA.17 trial, BCI (H/I) was shown to be predictive of extended endocrine therapy benefit. Letrozole treatment led to a reduction in the absolute risk of recurrence at 5 years of 16.5% in patients with high BCI (H/I) (P = .007) while there was no statistically significant benefit (P = .35) in patients with a low BCI (H/I) gene expression ratio.[14]

Although BCI has been clinically validated in prospective clinical trial cohorts, the health economic impact of BCI has not been investigated, particularly with respect to the novel functionality in predicting extended endocrine therapy benefit. BCI can be ordered at initial diagnosis to assess risk of overall, early, and late recurrence, and the likelihood of extended endocrine therapy benefit. In addition, BCI can be used in the prevalent population—those patients who are recurrence-free after approximately 5 years of endocrine-based therapy—to assess risk of late recurrence and likelihood of benefit from continued endocrine therapy. Therefore, the purpose of this study was to assess the health economic impact associated with implementing BCI at diagnosis or with utilizing BCI in patients who are recurrence-free 5 years after diagnosis and who are considering extended endocrine therapy.

METHODS

Models

A deterministic, decision-analytic model was developed from the payer perspective to project cost and clinical outcomes of using BCI compared with standard clinicopathologic evaluation to guide ER+, LN– breast cancer patient management for decisions of adjuvant chemotherapy and duration of endocrine-based therapy. Treatment of a hypothetical cohort of ER+, LN– breast cancer patients was simulated with patient flow models, the structures of which were developed according to the 2012 National Comprehensive Cancer Network guidelines for management of such patients.[7] Branches represented patient management under 2 scenarios: using standard clinicopathologic diagnostic modalities alone versus incorporating BCI. The hypothetical patient cohort was followed through the models that tracked costs across a variety of possible health states including adjuvant chemotherapy, complications, endocrine therapy, observation, recurrence, and death over a 10-year follow-up. Two separate models were developed: the first evaluated BCI ordered at diagnosis and included impact on adjuvant chemotherapy decision making and decision making regarding extended endocrine therapy; the second evaluated BCI when ordered at 5 years post diagnosis for the hypothetical population of patients who were recurrence-free at 5 years post diagnosis, and included impact on decision making for duration of endocrine-based therapy.

Clinical Inputs

Clinical Decision Making. Key assumptions driving adjuvant chemotherapy decision making are highlighted in Table 1. BCI risk categorization was derived from a real-world clinical validation cohort in the indicated patient population.[11] Clinical decision making based on risk categorization and estimates of disease-free survival were estimated based on published studies evaluating impact of Recurrence Score (21-gene assay).[3,15] Key assumptions driving use of extended endocrine-based therapy are also highlighted in Table 1. In the scenario without BCI, inputs were estimated based on interviews with disease-state experts. In the scenario with BCI, the model assumes that patients with high BCI (H/I) would

Table 1. Key Assumptions: Clinical Decision Making and Compliance

Adjuvant Chemotherapy Patient Flow				
Recurrence risk breakdown	**Recurrence Risk**			**Source**
Low risk	52.7%			[3]
Intermediate risk	34.6%			
High risk	12.7%			
10-year DRFS rrates	**ET**	**Chemo + ET**		
Low risk	96%	95%		[14]
Intermediate risk	88%	87%		
High Risk	49%	85%		
Chemotherapy treatment rates	**Without Test**	**With Test**		
Low risk	50%	10%		[3]
Intermediate risk	55%	36%		
High risk	60%	72%		
Extended Endocrine Therapy Patient Flow				
BCI (H/I) risk breakdown	**Recurrence Risk**			
BCI H/I low	60%			[11], [13]
BCI H/I high	40%			
Menopausal status	**At Diagnosis**	**5 years Post Diagnosis**		
Pre-menopausal	30%	9%		[16], Expert opinion
Postmenopausal	70%	91%		
Extended endocrine therapy utilization	**Without Test**	**BCI (H/I) Low**	**BCI (H/I) High**	
Pre-menopausal	28%	0%	100%	[22], Physician survey and expert opinion
Pre to postmenopausal	32%	0%	100%	
Postmenopausal	22%	0%	100%	
5-year disease-free survival	**Observation**	**Extended ET**		
BCI (H/I) low	87%	91%		[13]
BCI (H/I) high	73%	89.5%		
Compliance Impact				
Compliance rate	**Years 0-5**	**Years 6-10**		
Adherent	50%	61%		[15], [16]
Nonadherent	19%	11%		
Discontinued	31%	28%		
Increased recurrence risk		**Assumption**		
Adherent		1.0		[15]
Nonadherent		1.44		
Discontinued		1.61		
Increased compliance with BCI		**Assumption**		
Increase in Compliance		15%		[17], [18]

ET: Endocrine therapy; pre- to postmenopausal: patients that became menopausal during the first 5 years of endocrine therapy. BCI indicates breast cancer index; DRFS indicates distant recurrence free survival.

receive extended endocrine therapy, and patients with low BCI (H/I) would stop endocrine therapy after 5 years based on the published outcomes from the MA.17 study.[13] Disease-free survival in years 5 to 10 was modeled based on BCI risk categorization status and utilization of extended endo crine therapy as reported in the MA.17 cohort.[13]

Compliance. To account for the potential effect of patient compliance with endocrine therapy on the effect of therapy and the likelihood of recurrence, compliance to

Table 2. Key Assumptions: Patient Management Costs (ER+, LN– Breast Cancer)

Adjuvant Chemotherapy Mean Costs	Mean Cost		Source
Chemotherapy costs	$7305[a]		[3]
Supportive care costs	$9988[a]		
Adverse event costs	$1862[a]		
Total costs	$19,155[a]		
Follow-Up Mean Costs	**Cost**		
Annual follow-up costs	$504[a]		[19]
Adjuvant Endocrine Therapy Mean Costs	**Yearly Mean Cost**	**5-Year Mean Cost**	
Tamoxifen	$150	$750	[20]
Aromatase inhibitor	$682	$3025	
Recurrence Mean Costs	**Mean Cost**		
Total costs	$117,310[a]		[3]
BCI Test Mean Costs	**Mean Cost**		
BCI at diagnosis	$4950		Test manufacturer
BCI at 5 years post diagnosis	$3450		

[a]Costs adjusted for inflation based on reference year and data from the US Bureau of Labor Statistics.
BCI indicates breast cancer index.

endocrine therapy and the associated impact on disease recurrence was modeled according to previously observed rates.[16,17] The model also incorporated impact of a high BCI (H/I) on patient compliance, based on a published meta-analysis evaluating improvement in adherence following information interventions.[18,19] Compliance assumptions are highlighted in Table 1.

Costs. A variety of sources were used to build cost assumptions applied to patients as they moved through health states within the models (Table 2). Adjuvant chemotherapy costs were derived from an observational study in a Humana breast cancer population.[3] Follow-up and recurrence costs were based on breast cancer system economic studies and considered total cost to the payer including office visits, tumor-marker and imaging studies, systemic treatments, complication management, and end-of-life care.[3,20] Adjuvant endocrine drug costs were based on a RED BOOK analysis of average sale prices across various manufacturers, factoring in generic drug pricing for both tamoxifen and aromatase inhibitors.[21] Alongside endocrine therapy, additional costs associated with supportive care (ie, bisphosphonate therapy) and complications (ie, fractures) were included as well. Finally, the cost of the assay was based on the manufacturer's suggested retail pricing.

Analysis

For each model, impact on total cost was evaluated based on effect from adjuvant chemotherapy decision making, extended endocrine-based therapy decision making, and impact on compliance (Figure 1). One-way sensitivity analyses were conducted to evaluate the impact of parameter input uncertainty on model outcomes. Probabilities and cost parameters were varied over a range of clinically relevant conservative and aggressive estimates.

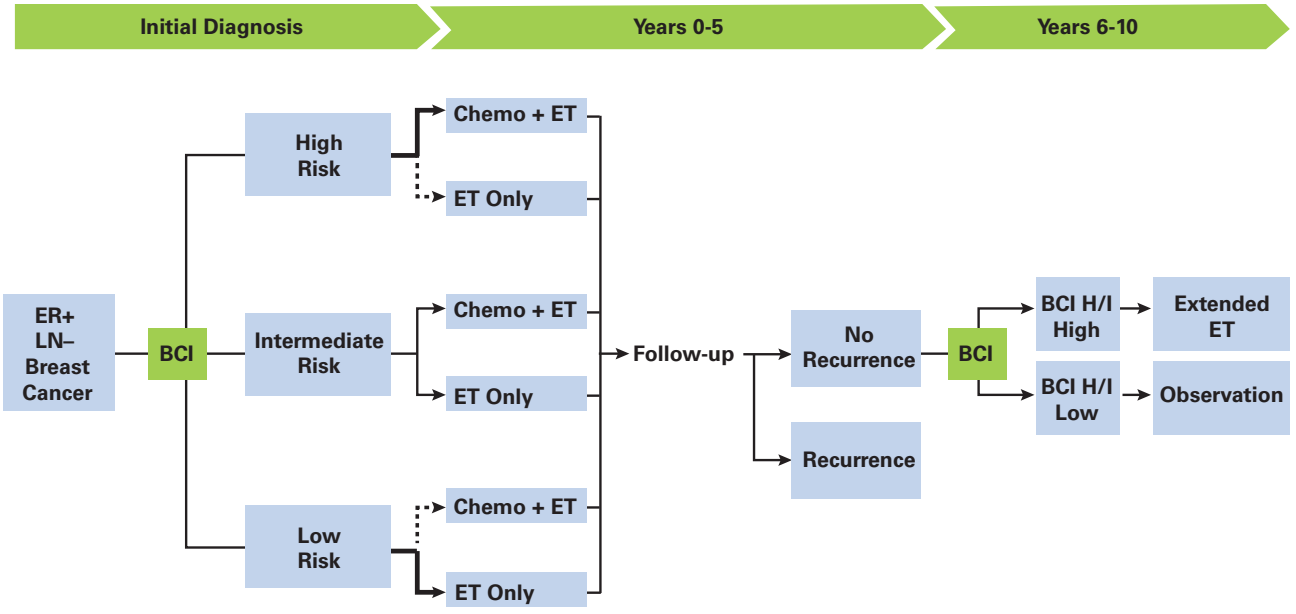
RESULTS

Model: BCI at Diagnosis

The base case model representing treatments based on standard clinicopathologic variables and 10 years of follow-up resulted in mean costs of $45,437 per patient. Use of BCI at diagnosis resulted in mean costs of $41,634, resulting in an average savings of $3803 per patient tested after accounting for the cost of the test. These savings can be traced to individual contributing cost drivers including targeted use of adjuvant chemotherapy, targeted use of extended endocrine therapy, and increased patient compliance (Figure 2A).

Key outputs of the sensitivity analysis are illustrated in Figure 3A. The model was most sensitive to the percentage of patients classified as BCI (H/I) high, to BCI test cost, and to the percentage of BCI (H/I) high patients receiving extended endocrine therapy. None of the sensitivity analyses resulted in cost savings of less than $2800 per patient tested, while more aggressive scenarios (eg, percentage of patients classified as BCI (H/I) high, and cost of recurrence) predicted cost savings of over $4000 per patient tested.

Figure 1. Patient Flow Decision Tree



This figure illustrates the treatment flow for ER+, LN– breast cancer patients whose management incorporates BCI. BCI information may be used at initial diagnosis to guide use of adjuvant chemotherapy and/or may be used 5 years post diagnosis to guide use of extended endocrine therapy. BCI/HI indicates Breast Cancer Index/HOXB13:IL17BR ratio; chemo, chemotherapy; ER+, LN–, estrogen receptor-positive, lymph node-negative; ET, endocrine therapy.

Model: BCI at 5 Years Post Diagnosis

In the second model, evaluating use of BCI in patients who were recurrence-free at 5 years post diagnosis and initial therapy, the base case resulted in mean costs of $22,708 per patient without the use of BCI. Use of BCI at this time point resulted in mean costs of $20,904, resulting in a savings of $1803 per patient after accounting for the cost of the test (**Figure 2B**). The cost benefit was predominantly driven by targeted use of extended endocrine therapy ($5194 savings per patient).

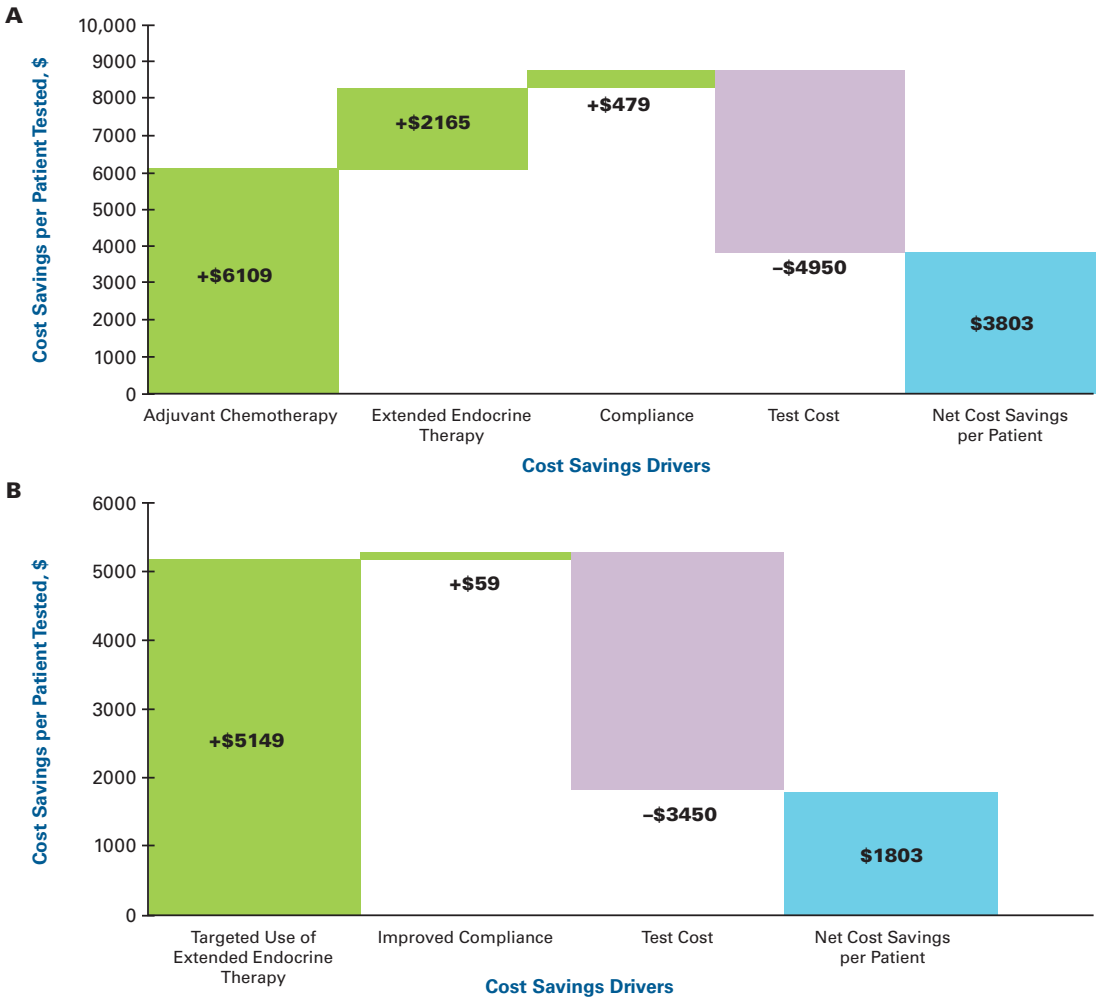
Key outputs of the sensitivity analysis for this model are illustrated in **Figure 3B**. The model was most sensitive to the percentage of patients classified as BCI (H/I) high, to the percentage of BCI (H/I) high patients receiving extended endocrine therapy, and to the total cost of a recurrence. None of the sensitivity analyses resulted in a cost savings under $300 per patient tested, while more aggressive scenarios (eg, percentage of patients classified as BCI (H/I) high, and cost of recurrence) predicted cost savings of over $2300 per patient tested.

DISCUSSION

This health economic model projects the impact on patient management and healthcare cost of a second-generation molecular test for breast cancer recurrence risk in patients with ER+, LN– breast cancer. The study has 2 primary findings. First, the ability of BCI to predict likelihood of benefit from extended endocrine therapy adds additional cost savings on top of those cost savings previously described for first-generation assays evaluating the impact on adjuvant chemotherapy decision making alone.[3,19] BCI is projected to save an additional $2644 per patient above the cost savings associated with optimizing adjuvant chemotherapy alone. Second, the study demonstrated that use of BCI in patients who are recurrence-free after 5 years is cost saving as well. Optimizing the use of extended endocrine therapy in these patients is projected to save $1803 per patient tested after accounting for the test cost in this setting.

As discussed, BCI has been estimated to save additional costs beyond optimization of adjuvant chemotherapy, the majority of which is driven by optimization of extended endocrine therapy. Several large, randomized, prospective clinical trials (eg, MA.17, ATLAS, aTTom) have recently brought significant attention to the decision of whether to extend endocrine therapy. While these trials demonstrated treatment benefit, they showed only a small absolute benefit in recurrence rates with extended endocrine therapy in the unselected population.[8-10] Given

Figure 2. (A) BCI at Diagnosis—Cost Savings Map and B) BCI at 5 Years Post Diagnosis—Cost Savings Map



(A) highlights the cost savings associated with incorporating BCI at diagnosis. Average cost savings are generated from multiple components (in green), which are then modified by the cost of the test (in pink) to yield an average net cost savings per patient tested over the 10-year period post diagnosis (in blue). (B) highlights the cost savings associated with incorporating BCI once 5 years have passed after initial diagnosis and the decision whether to extend endocrine therapy is imminent. Average cost savings are generated from multiple components (in green), which are then modified by the cost of the test in this setting (in pink) to yield an average net cost savings per patient tested (in blue) over the 5-year period after test utilization (10 years after initial diagnosis).

the significant toxicities and side effects associated with endocrine therapy, there exists an unmet need to identify which patients should receive extended endocrine therapy based on a higher risk of recurrence and likelihood of benefit.[22,23] BCI may be a tool to help address this unmet need by stratifying patients based on their risk of recurrence and likelihood of benefit, thereby increasing extended endocrine therapy use in patients expected to derive the most benefit while avoiding further treatment and minimizing drug-related side effects in patients who are unlikely to receive benefit. The results of this study indicate that this additional clinical value proposition translates into further system economic benefit for this assay. With generic aromatase inhibitors now available, extended endocrine therapy is highly cost effective and substantially reduces recurrences in patients with high BCI (H/I).

The magnitude of the cost savings generated by optimization of extended endocrine therapy depends on when the assay is used over the course of diagnosis and follow-up. When used at initial diagnosis, this clinical value proposition adds an additional $2165 to the per patient tested cost savings. When used for recurrence-free patients at 5 years post diagnosis (the decision point for extending endocrine therapy), this clinical value proposition adds $5194 to the per patient cost savings. The per patient tested cost benefit is greater when the test is used at 5 years post diagnosis because it is only used in the

■ **Figure 3.** (A) BCI at Diagnosis—Univariate Sensitivity Analysis (B) BCI at 5 Years Post Diagnosis—Univariate Sensitivity Analysis

(A) Tornado diagram illustrates sensitivity of the model.
(B) Tornado diagram illustrates the sensitivity of the model.
BCI indicates breast cancer index; Ext ET indicates extended endocrine therapy; pre- to postmenopausal, patients that became menopausal during the first 5 years of endocrine therapy.

subset of women who are eligible for extended endocrine therapy (ie, not including women who have a recurrence or discontinuation within the first 5 years), and therefore do not realize the additional savings due to this component of the test.

This study has a number of limitations. First, as an *in silico* modeling study, many assumptions were based on published clinical literature and expert interviews rather than prospective real-world data of test economic impact. As was the case with first-generation breast cancer risk recurrence assays, future studies must assess the impact of the assay in collaboration with third-party payers to illustrate cost savings in a real-world setting. Second, sensitivity analyses highlighted that cost savings were

most sensitive to the cost of the assay, to the proportion of patients classified as high BCI (H/I), and to the percentage of those patients following the recommendation to receive extended endocrine therapy. The base scenario of the model assumes optimal alignment between test recommendation and physician/patient decision on extended endocrine therapy. As has been observed in real-world studies of first-generation assays, test recommendations are incorporated with other clinical and patient-specific factors, and thus are not followed in all cases. Furthermore, it is important to note that the model assumed that physicians may treat post menopausal patients with extended aromatase inhibitor therapy following an initial 5 years of aromatase inhibitor therapy. This assumption was directly informed by interviews with disease-state experts, per the study methodology. While definitive data on the effectiveness of 10 years of aromatase inhibitor treatment versus 5 years is not yet available, the assumption is based on the effectiveness of extended endocrine therapy demonstrated in 4 different randomized, clinical trials.[8-11] These assumptions and limitations should be a focus for ongoing real-world studies. However, it is important to note that the sensitivity analysis reveals that even with a 20% discrepancy between test recommendation and patient management, the test remains highly cost-effective. Third, in a rapidly evolving therapeutic landscape such as that of breast cancer treatment, it is difficult to fully characterize the downstream costs of recurrent cancer, as the treatment landscape will likely involve new therapies by the time this patient cohort experiences recurrences. With the emergence of new higher-priced targeted therapy for metastatic disease, costs for patients with recurrent breast cancer are likely to rise.[24,25] To examine this limitation, sensitivity analyses revealed that as the cost of breast cancer recurrence increases, BCI cost-effectiveness increases. Given these trends, the base case assumes a relatively conservative value for recurrence costs based on recent data, leaving room for potential upside as treatment costs rise. Finally, clinical data evaluating the benefit of adjuvant chemotherapy based on BCI risk stratification are not available, thus assumptions related to chemotherapy utilization and patient outcomes are modeled based on published RS studies. Notably, BCI has been investigated in a neoadjuvant chemotherapy study, and demonstrated ability to predict response to chemotherapy (as assessed by pathologic complete response).[26] In addition, the sensitivity analyses demonstrate that a reduction in chemotherapy benefit predictability of 25% results in only a minor decrease in cost savings. Thus, while this is an important limitation of the study, it is unlikely to significantly alter the study's conclusions.

In conclusion, this health economic analysis demonstrates that use of BCI in patients with ER+, LN– early breast cancer is cost saving compared with management without the use of a molecular assay. From a third-party payer perspective, use of this test may result in substantially lower overall medical costs. These cost savings are primarily driven by a reduction in adjuvant chemotherapy in patients unlikely to derive benefit and an increase in extended endocrine therapy utilization in patients likely to receive substantial benefit. Additional studies on clinical practice in real-world populations are needed to validate these results.

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