Economic Analysis of Targeting Chemotherapy Using a 21-Gene RT-PCR Assay in Lymph-Node–Negative, Estrogen-Receptor–Positive, Early-Stage Breast Cancer

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Objective: To appraise the economics of a recurrence score (RS), based on an assay that predicts distant recurrence-free survival in lymph-node–negative (LN–), estrogen-receptor–positive (ER+) patients with early-stage breast cancer receiving tamoxifen.

Study Design: Cost-utility analyses using a decision analytic model.

Methods: Using a Markov model, we forecast overall survival, costs, and cost effectiveness of using the RS in patients classified as having low or high risk of distant recurrence based on National Comprehensive Cancer Network (NCCN) clinical guidelines. Data from a large multicenter clinical trial (NSABP B-14) were analyzed to derive risk classification based on guideline criteria and RS assignments. Efficacy of adjuvant chemotherapy (CT) on distant recurrence-free survival (DRFS) was based on published meta-analyses of CT trials. The analysis took a societal perspective, considering survival, quality of life, and relevant costs.

Results: Fifty-three patients (8%) were classified as having low risk of distant recurrence by NCCN guidelines and the RS reclassified 15 of these patients (28%) to an intermediate/high-risk group. The remaining 615 patients (92%) were classified at high risk of distant recurrence by NCCN guidelines and the RS reclassified 300 of these patients (49%) to a low-risk group. Among a hypothetical cohort of 100 patients, RS is predicted on average to increase quality-adjusted survival by 8.6 years and reduce overall costs by $202 828. RS was cost saving in more than two-thirds of probabilistic simulations, with cost effectiveness most influenced by the propensity to administer CT based on RS results, and by the proportion of patients at low risk as defined by NCCN guidelines.

Conclusions: The RS predicts more accurately than current guidelines recurrence risk in LN–, ER+ patients with early-stage breast cancer. If applied appropriately, the assay is predicted to increase quality-adjusted survival and save costs.

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More than 210 000 women in the United States are diagnosed each year with breast cancer.[1] Breast cancer remains among the most common cancers in women, and the most common cause of death among women between the ages of 40 and 79.[1]

Several large randomized clinical trials demonstrated the benefit of hormonal therapy in patients with estrogen-receptor–positive (ER+) early-stage breast cancer (ESBC).[2] An important decision for a patient with lymph-node–negative (LN–), ER+ ESBC is whether to also undergo adjuvant chemotherapy after primary surgery to prevent or delay distant recurrence.[3-7] Consensus guidelines endorse the addition of adjuvant chemotherapy for LN–, ER+ cancer for patients up to 70 years old, or older if they are medically fit.[8-11] Experts also recommend against routine use of adjuvant chemotherapy for small tumors (<1 cm) or for small tubular or mucinous tumors.[12]

Enhanced public health efforts to detect breast cancer, such as mammographic screening, have increased early-stage detection.[13,14] The success of this campaign has naturally resulted in physicians and patients increasingly facing a complex question: do the benefits of adjuvant chemotherapy outweigh the medical risks and known adverse effects on quality of life?[15] That this question is difficult to answer is supported by recent evidence showing wide variation in the propensity to prescribe adjuvant chemotherapy, a variation that cannot be explained by characteristic risk factors such as age, tumor size, and histology.[10,16-21] An active area of oncology research therefore is identifying additional reliable predictors of recurrence in ESBC that would assign risk more accurately and help guide the decision to prescribe adjuvant chemotherapy.[22-27]

A 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (Onco*type* DX Breast Cancer Assay, Genomic Health, Inc, Redwood City, Calif) gen-

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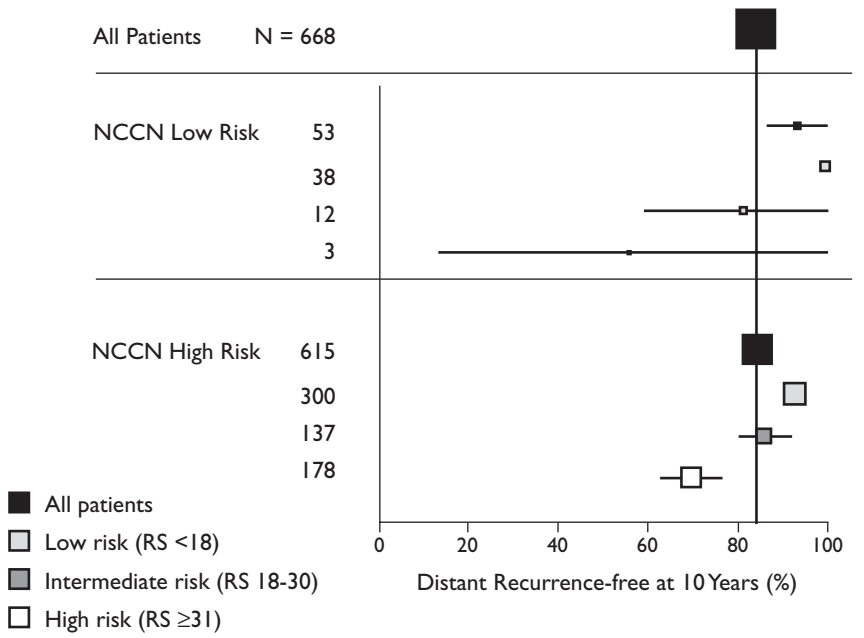
Figure 1. Distant Recurrence-free Survival at 10 years, by NCCN Risk Status and Recurrence Score



As described by NCCN (v.1.2005), lymph-node–negative (LN–) tumors with unfavorable prognostic features (ie, high risk) warranting consideration for systemic adjuvant chemotherapy are (1) invasive ductal or lobular LN– tumors 0.6 to 1 cm in diameter that include angiolymphatic invasion, high nuclear grade, high histologic grade, HER-2 overexpression, or hormone-receptor-negative status, or (2) tumors more than 1 cm in greatest diameter.[48]
NCCN indicates National Comprehensive Cancer Network; RS, recurrence score.
Data reproduced with permission from Paik et al.[29]

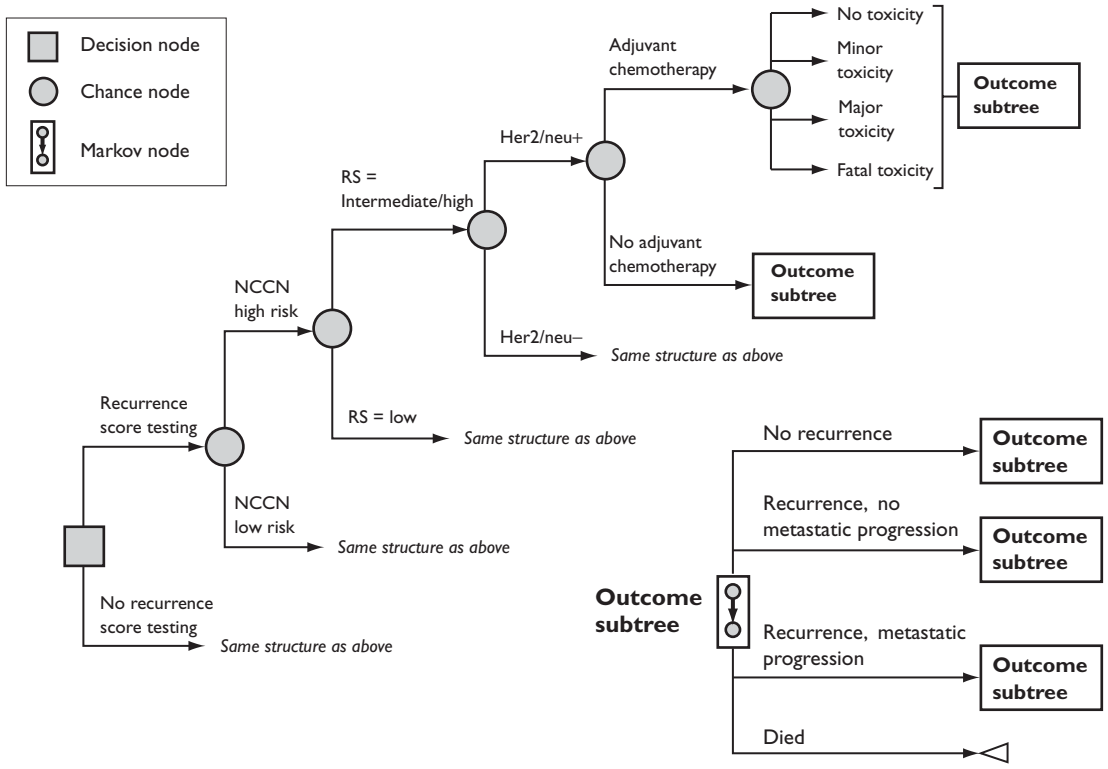
erates an individualized "recurrence score" that is derived from a proprietary algorithm. The recurrence score has been prospectively validated as a predictor of 10-year distant recurrence-free survival (DRFS) in patients with LN–, ER+ ESBC.[28] The investigators obtained tissue samples from 668 LN–, ER+ patients who were treated with tamoxifen in the National Surgical Adjuvant Breast Cancer Project (NSABP) B-14 clinical trial from 1982 through 1988 and whose outcomes have been tracked over time by NSABP sites. The recurrence score accurately classified patients into low and high risk of DRFS ($P < .001$).[28] When the recurrence score was examined together with age and tumor size in a multivariate analysis, only recurrence score remained a significant predictor of DRFS at 10 years ($P < .001$).[28] The study also confirmed the relatively poor reliability of current risk stratification. Twelve of 53 (22%) patients initially classified by National Comprehensive Cancer Network (NCCN) criteria as low risk were reclassified by the recurrence score as intermediate risk and had a 10-year DRFS equal to 82% (95% confidence interval [CI] 60%-100%); 3 (6%) patients were reclassified as high risk and had a 10-year DRFS equal to 57% (95% CI 1%-100%) (**Figure 1**).[29] Conversely, 300 of 615 (49%) patients assigned by NCCN criteria as high risk for recurrence were reclassified by the recurrence score as low risk and had a 10-year DRFS equal to 92% (95% CI 89%-95%).

Although the recurrence score has been subjected to clinical validation, questions necessarily arise about its affordability and factors that would influence its appropriate use. The purposes of this study were (1) to estimate the incremental benefits, costs, and cost effectiveness of using the recurrence score to better assign risk of DRFS associated with ESBC, and (2) to assess the factors that most influence potential benefits and efficient use of the recurrence score.

METHODS

This evaluation focused on the recurrence score and not other RT-PCR or genomic assays under development, because the analyses depend critically on the quality of evidence and detailed findings of the validation studies described herein. We present DRFS, overall survival (OS), and relevant costs associated with use of the recurrence score to reclassify risk of recurrence compared with risk classification using current NCCN guidelines alone. Outcomes were evaluated using a common framework for health economic appraisals, called the Markov model (**Figure 2**), which provides a convenient way of modeling prognosis.[30] In a Markov model, a patient may be in 1 of a finite number of states of health, and events of interest are modeled as transitions from one state to another. For each state, analysts assign a utility as an adjustment factor for quality of life. Utility weights typically range from 0 to 1, in which 0 represents a state as bad as death, 1 represents perfect health, and the values between 0 and 1 represent degrees between these extremes. The contribution to total utility, commonly referred to as quality-adjusted life years (QALYs), of a particular state consists of the length of time spent in a state multiplied by the utility of that state.

Figure 2. Diagram of Recurrence Score Assay for Assigning Risk in Early-stage Breast Cancer



NCCN indicates National Comprehensive Cancer Network; RS, recurrence score.

Two scenarios were considered involving representative patients with LN–, ER+ ESBC who were expected to receive 5 years of hormonal therapy. In scenario 1, patients were classified by NCCN as low risk (eg, tumor size <1 cm), would therefore not receive chemotherapy, and would have a predicted 10-year probability of recurrence of 7.8% based on analyses of NSABP B-14 data (**Table 1**). In scenario 2, patients were classified by NCCN as high risk (eg, tumor size >2 cm), would therefore be recommended to receive chemotherapy, and would have a predicted 10-year probability of recurrence of 21.9%.

The recurrence score was assumed to reclassify recurrence risk independent of NCCN risk criteria, with the probability of reclassification based on results of the NSABP B-14 data. In the base case, we assumed that all patients assigned as intermediate/high risk by the recurrence score would undergo chemotherapy and all patients assigned as low risk by the recurrence score would not receive chemotherapy. We explored in sensitivity analysis the implications of different probabilities of chemotherapy use based on risk classification by the recurrence score. The model tracked rates of recurrence and death, as shown in the outcome subtree of the decision tree in Figure 2.

Probability of Risk Reclassification

The NSABP provided us with analyses of B-14 data to determine the risk of recurrence based on NCCN criteria and on the recurrence score results (Figure 1 and **Table 2**).[29] For the 53 (7.9%) women assigned as having low risk for recurrence based on NCCN criteria, NSAPB B-14 showed a 28% (95% CI 16.8%-42.4%) probability of reclassification to intermediate/high risk (15 of 53 women) with the recurrence score. For the other 615 (92.1%) women assigned as having high risk for recurrence based on NCCN criteria, NSABP B-14 showed a 49% (95% CI 44.5%-52.6%) probability of reclassification to low risk (300 of 615 women) based on the recurrence score.

Risk of Recurrence and Death

Annual risks of recurrence and survival were obtained from published meta-analyses of clinical trials (Table 1).[31] The relative risk reduction of distant recurrence associated with chemotherapy plus tamoxifen

Table 1. Probabilities

Model Parameter	Base Case Value, %	Range Tested in Sensitivity Analyses, %	Data Source
Probability of distant recurrence by 10 years			
If high risk by NCCN criteria	21.9	Change by ± 50%	Ref 31
If low risk by NCCN criteria	7.8	Change by ± 50%	Ref 31
Propensity to change treatment due to risk reclassification based on RT-PCR result			
If intermediate/high risk by recurrence score	100	50-100	Assumption
If low risk by recurrence score	100	50-100	Assumption
RRR of distant recurrence with chemotherapy			
If intermediate/high risk by recurrence score	15	10-20	Ref 31
If low risk by recurrence score	45	30-60	Ref 31
Probability of response to MBC treatment after primary response			
If Her2/neu–	38.0		Ref 32
If Her2/neu+	54.0		Ref 32
Probability of metastatic progression after distant recurrence			
If response to MBC treatment, Her2/neu–	59.7		Ref 32
If response to MBC treatment, Her2/neu+	53.7		Ref 32
If nonresponse to MBC treatment, Her2/neu–	98.3		Ref 32
If nonresponse to MBC treatment, Her2/neu–	88.5		Ref 32
Probability of death after distant recurrence, annual			
If Her2/neu–	40.0	20-60	Ref 32
If Her2/neu+	37.2	20-60	Ref 32
Probability of chemotherapy toxicity			
Minor	60	Change by ± 50%	Refs 33, 34
Major	5	Change by ± 50%	Refs 33, 34
Fatal	0.5	Change by ± 50%	Refs 33, 34
Cancer HER2/neu+	25	20-30	Ref 32

MBC indicates metastatic breast cancer; NCCN, National Comprehensive Cancer Network; Ref, reference number; RRR, relative risk reduction; RT-PCR, reverse-transcription–polymerase chain reaction.

versus tamoxifen only is approximately 30%, and is assumed to be the same regardless of NCCN risk classification.[31] Studies are ongoing to assess the correlation of tumor gene expression and response to chemotherapy.[35] Gianni et al recently reported that gene expression profiles of paraffin-embedded core biopsy tissue predicted response to chemotherapy in patients with locally advanced breast cancer,[36] which was subsequently confirmed in an NSABP study.[37] In the base case model, we assumed a 15% risk reduction associated with chemotherapy if the recurrence score falls in the low-risk category and a 45% risk reduction associated with chemotherapy if the recurrence score falls in the intermediate/high-risk category.

After recurrence, the chemotherapeutic regimen, probability of response, and risk of further disease progression depend on Her2/neu status, assumed to be positive in 25% of cancers.[32] Regardless of response, the rate of disease progression is lower for patients with Her2/neu-positive tumors receiving combination trastuzumab/paclitaxel than for patients with Her2/neu-negative tumors receiving paclitaxel monotherapy. The annual probability of death after progression is approximately 40%.[32]

Quality of Life

Previous studies have reported a relatively high utility of 0.98 after initial chemotherapy for ESBC (**Table 3**).[38] To account for emerging data on late negative effects of early treatment, such as potential recurrence or late effects of hormonal and chemotherapy, we lowered this value in sensitivity analyses.[45,46] We used published estimates of the negative impact on utility for recurrence (recently used by Elkin et al to assess implications of newer strategies for patients with advanced breast cancer).[32] Large variability

exists on how breast cancer survivors report their perceptions of the value of chemotherapy therapies.[39,47] For example, in a recent study, among survivors *not* receiving chemotherapy, 61% reported they would have chosen chemotherapy if it offered at least a 6% reduction in breast cancer mortality.[39] By contrast, 97% of survivors who *had* received chemotherapy would choose chemotherapy if it offered at least a 6% reduction in breast cancer mortality.[39] Cole et al showed the implications of chemotherapy on quality-adjusted survival over a range of utilities, using 0.5 as an illustrative value.[31] We found in preliminary analyses that use of chemotherapy in low-risk patients yields no gain in QALYs when the utility of chemotherapy is set to 0.5 for 6 months of treatment. We applied this utility to chemotherapy, such that findings of the base case model would be consistent with current guideline recommendations for use of chemotherapy in the adjuvant setting.

Table 2. Risk Classification by NCCN Criteria and Recurrence Score Results

	Recurrence Score, n (%)		
NCCN Criteria	Low Risk	Intermediate/High Risk	Total, n (%)
Low risk	38 (5.7)	15 (2.2)	53 (7.9)
High risk	300 (44.9)	315 (47.2)	615 (92.1)
Total	338 (50.6)	330 (49.4)	668 (100)

NCCN indicates National Comprehensive Cancer Network.
Source: National Surgical Adjuvant Breast Cancer Project (NSABP) B-14.

Costs

Cost of the assay was based on the manufacturer's suggested retail price of $3450. Drug acquisition costs for chemotherapy were based on 2004 Redbook prices (Table 3).[40] Estimates of adjuvant chemotherapy costs vary depending on the type of regimen used. For example, regimens that include taxanes are more costly than regimens using only anthracycline and cyclophosphamide (also known as AC) or methotrexate and 5-fluorouracil (also known as CMF). Surveys of medical oncologists have demonstrated that taxane-based regimens are used more frequently in patients with Her2/neu-positive tumors.[48] We included costs associated with infusion, patient time, use of colony-stimulating factors to prevent myelosuppressive complications, and management of chemotherapy-related side effects. Oncologists have reported that approximately 50% of patients with ESBC receive an eythropoietic-stimulating factor or a myeloid colony-stimulating factor.[48]

We reviewed the literature to determine the cost of cancer recurrence surveillance in patients with ESBC. Simon et al. retrospectively evaluated the costs of routine surveillance in patients treated for ESBC, including outpatient visits, laboratories, and imaging studies,[49] which remain the approach recommended by guidelines.[41] They reported a cost of $1396 over 5 years in 1993 dollars. This results in an average annual cost, inflated to 2004 dollars, of $421.

A search of the medical literature (MEDLINE, CANCERLIT) revealed several studies that reported the costs in the last year of life for elderly Medicare beneficiaries, varying between $23 000 and $37 000.[42-44] We applied an average cost of $30 000 for end-of-life care.

Other Policy Assumptions and Analyses

The model takes a societal perspective, including relevant costs and outcomes associated with breast cancer. We forecasted outcomes over the patient's lifetime, as recommended in guidelines for economic appraisals of medical technologies.[42-44] In sensitivity analyses, we explored the implications of shorter forecast durations. The cycle length of the model was 1 year, and 10-year recurrence rates were used to estimate annual rates in the model assuming a constant hazard rate over 10 years. Several factors may have influenced the effect of recurrence score testing on QALYs and costs. We conducted a series of sensitivity analyses to explore what factors had the greatest influence on these end points, and on costs per QALY gained. Although we examined each variable, we focused on several variables that we predicted a priori would have more influence on these end points, such as (1) the propensity to change chemotherapy decision based on recurrence score, (2) relative risk reduction of chemotherapy plus tamoxifen versus tamoxifen only, (3) cost of chemotherapy, and (4) the proportion of patients defined by NCCN criteria as low risk. Using standard methodologies, we discounted both costs and survival by a fixed annual rate of 3%.[50]

Incremental cost utility was estimated according to a standardized method described in published guidelines as the difference in cumulative costs between testing and no testing with the recurrence score, divided by the difference in years of quality-adjusted survival between the 2 approaches. We show outcomes for risk scenarios first separately and then applied to a cohort of 100 patients.

Table 3. Costs and Health-state Utilities*

	Base Case Value	Range Tested in Sensitivity Analyses	Data Source
Health-state utilities			
After chemotherapy, no distance recurrence	0.98	0.9	Ref 38
Recurrence			
If respond to chemotherapy for advanced breast cancer	0.84	Change by ±15%	Ref 32
Stable	0.70	Change by ±15%	Ref 32
Progressive	0.49	Change by ±15%	Ref 32
Associated with chemotherapy, 6 months only	0.50	0.25-0.80	Refs 31, 39
Death	0	NA	
Costs, $			
Chemotherapeutic drugs, per course			
Adjuvant chemotherapy			
Her2/neu–	15 123	Change by ±15%	Ref 40
Her2/neu+	17 736	Change by ±15%	Ref 40
Metastatic disease, per course			
Paclitaxel	17 068	Change by ±15%	Ref 32
Herceptin	30 519	Change by ±15%	Ref 32
Other chemotherapy costs			
Premedication, per infusion	12	Change by ±15%	Ref 32
Travel, per infusion	11	Change by ±15%	Ref 32
Patient time, per hour	6	Change by ±15%	Ref 32
Oncology visit	36	Change by ±15%	Ref 32
Treatment of side effects			
Minor	2400	Change by ±15%	Refs 33, 34
Major	15 700	Change by ±15%	Refs 33, 34
Fatal	39 000	Change by ±15%	Refs 33, 34
Monitoring for side effects			
Primary cancer surveillance if no distant recurrence, per year	421	200-1000	Ref 41
Progressive metastatic disease, per year	4680	3500-6000	Ref 32
End-of-life	30 000	23 000-37 000	Refs 42-44

Ref indicates reference number.
*Utilities is a unitless measure, scaled from 0-1.

We conducted extensive 1- and 2-way sensitivity analyses on the model assumptions. Ranges used in these analyses are shown in Tables 1 and 3. Last, we conducted a probabilistic analysis (Monte Carlo) to determine the effect of uncertainty in all variables on the cost-utility ratio for the cohort. A technical appendix with detailed information on these simulations is available to readers upon request of the corresponding author.

RESULTS

Cost Effectiveness of Chemotherapy Based on NCCN Guidelines

Administration of adjuvant chemotherapy in high-risk patients based only on NCCN guidelines was forecast to increase overall survival by 1.53 years and increase QALYs by 0.65 years. Adjuvant chemotherapy increases overall costs for breast cancer by $13 878, resulting in a cost utility equal to $21 428 (**Table 4**). In low-risk patients, adjuvant chemotherapy was forecast to increase overall survival, but only by 0.37 years compared with use of chemotherapy in high-risk patients. However, when adjusting for adverse consequences on quality of life of chemotherapy, quality-adjusted survival with chemotherapy is lower than without chemotherapy. The model findings therefore are consistent with current NCCN guidelines that adjuvant chemotherapy improves overall survival and QALYs for patients at high risk of recurrence, but has a net negative effect on QALYs for patients at low risk of recurrence.

Cost Effectiveness of Reclassifying Patients Using the Recurrence Score

Using the recurrence score to reclassify NCCN-defined low-risk patients to intermediate/high risk was projected to add $15 776 per patient for chemotherapy. Another $12 190 in testing costs was expected per patient reclassified as intermediate/high risk (**Table 5**). Chemotherapy administered to patients at intermedi-

ate/high risk has an expected increase of 1.86 years in overall survival. The cost per QALY gained of using the recurrence score to reclassify NCCN-defined low-risk patients was calculated as $31 452.

Reclassifying a patient with NCCN-defined high-risk ESBC to low risk based on the recurrence score will save costs by foregoing administration of chemotherapy. An average of 2 NCCN-defined low-risk patients must be tested to reclassify 1 patient; hence, the assay cost per patient reclassified was $7073. Because these patients are now classified as having a low risk of recurrence, avoiding chemotherapy is predicted to increase quality-adjusted survival and save $8947 (SD $302) in lifetime costs.

Among a group of 100 patients with LN–, ER+ ESBC (7.9% of whom are NCCN-classified as low risk for distant recurrence), use of the recurrence score was expected to reclassify 2 patients from low to intermediate/high risk and 45 patients from high to low risk. Assuming that patients at intermediate/high risk receive chemotherapy and patients at low risk do not receive chemotherapy, testing will increase QALYs in this cohort by 8.6 years (**Table 6**). Use of the recurrence score in 100 patients will cost $345 000; the cost of adjuvant chemotherapy will decrease by 46%, from $1.63 million to $876 000. Overall costs were projected on average to decline by 5%, from $4.32 million to $4.12 million, for a net savings of $202 828.

Sensitivity Analyses

In 1-way sensitivity analyses (**Table 7**), recurrence score testing was beneficial and cost saving using alternative assumptions for most of the variables. The 2 exceptions were (1) the propensity to not use chemotherapy if the recurrence score reclassified patients from high to low risk and (2) the proportion of patients tested with the recurrence score who were low risk by NCCN criteria. If only 50% of high-to-low reclassified patients were to forego chemotherapy, then the test would be cost increasing; the cost per QALY gained would be $17 234. Testing only NCCN-defined high-risk patients has a minimal effect on QALYs, but results in larger cost savings. Testing only NCCN-defined low-risk patients will have larger benefit in QALYs and be cost increasing, with a cost utility of $31 529.

The QALYs gained with recurrence score testing were relatively unchanged from the base case except for situations in which the effect of chemotherapy on quality of life was substantial (eg, when setting loss in utility associated with chemotherapy as low as 0.1). Costs unrelated to chemotherapy drug acquisition, such as those for infusions, management of emesis and other adverse events, and use of colony-stimulating factors, had the largest effect on differences in costs. Cost savings associated with recurrence score testing were attentuated in scenarios with low nonchemotherapy drug costs, such as if few patients receive colony-stimulating factors. Alternatively, if nonchemotherapy drug

Table 4. Cost Effectiveness of Chemotherapy Using NCCN Criteria

	Low Risk (NCCN)			High Risk (NCCN)		
	No Chemotherapy	Chemotherapy	Difference	No Chemotherapy	Chemotherapy	Difference
10-y DRFS, %	92	93	1	70	77	7
10-y OS, %	94	95	1	79	84	5
DRFS, y (mean)	33.09	33.51	0.42	20.74	22.39	1.66
OS, y (mean)	33.68	34.06	0.37	23.19	24.72	1.53
QALY, y (mean)	20.12	20.08	–0.04	14.82	15.47	0.65
Costs, $						
Adjuvant chemotherapy	0	15 776	15 776	0	15 776	15 776
Follow-up	23 310	22 820	–490	37 918	36 020	1898
Total	23 310	38 596	15 287	37 918	51 796	13 878
Cost effectiveness, $						
Per LYG			40 796			9084
Per QALY			No benefit			21 428

DRFS indicates distant recurrence-free survival; LYG, life-years gained; NCCN, National Comprehensive Cancer Network; OS, overall survival; QALY, quality-adjusted life years.

Table 5. Cost Effectiveness of Reclassifying a Patient With RT-PCR

	If Reclassified as Intermediate/High Risk			If Reclassified as Low Risk		
	No RT-PCR	RT-PCR	Difference	No RT-PCR	RT-PCR	Difference
10-y DRFS, %	78	86	8	93	92	–1
10-y OS, %	84	90	5	94	94	0
DRFS, y (mean)	24.52	26.56	2.04	33.30	33.09	–0.21
OS, y (mean)	26.47	28.33	1.86	33.87	33.68	–0.19
QALY, y (mean)	16.52	17.33	0.81	20.03	20.18	0.15
Costs, $						
Adjuvant chemotherapy	0	15 776	15 776	15 776	0	–15 776
Follow-up	33 507	31 163	–2344	23 310	23 066	–244
Test	0	12 190	12 190	0	7073	7073
Total	33 507	59 129	25 623	39 086	30 138	–8947
Cost effectiveness, $						
Per LYG			13 786			Cost saving
Per QALY			31 452			Cost saving

RT-PCR indicates reverse-transcriptase–polymerase chain reaction ; DRFS, distant recurrence-free survival; LYG, life-years gained; NCCN, National Comprehensive Cancer Network; OS, overall survival; QALY, quality-adjusted life years.

Table 6. Cost Effectiveness of Recurrence Score Assay Applied to Cohort of 100 Patients With LN–, ER+ Early-Stage Breast Cancer

	No RS Assay	RS Assay	Difference
Patient years			
DRFS	2836	2831	–4.85
OS	2976	2972	–4.21
QALYs	1814	1822	8.60
Costs, $			
Adjuvant chemotherapy	1 632 835	876 155	–756 680
Follow-up	2 687 542	2 896 394	208 852
Test	0	345 000	345 000
Total	4 320 377	4 117 549	–202 828

DRFS indicates distant recurrence-free survival; ER+, estrogen-receptor–positive; LN–, lymph-node–negative; OS, overall survival; QALY, quality-adjusted life years; RS, recurrence score.

costs are 25% higher, cost savings are even greater. Including the cost of patient travel and lost work productivity, equal to $17 per infusion,[32] also makes recurrence score testing more cost saving.

The base case evaluation used NCCN criteria to assess risk of distant recurrence. Other guidelines have been published and, for the most part, contain similar classification criteria, including tumor size, age, histology, and hormonal status.[9,51] Analyses of NSABP B-14 data using the criteria of other guidelines therefore would have relatively little impact on the cost utility of the recurrence score assay.

The probability of being reclassified as low risk and not receiving chemotherapy is a more significant driver of cost effectiveness than the probability of being reclassified as intermediate/high risk and receiving chemotherapy. The cost effectiveness of the recurrence score in a hypothetical cohort of patients was calculated as less than $50 000 per QALY gained if the propensity to use chemotherapy when recurrence score reclassifies a patient as low risk is at least 30%. Recurrence score is cost saving when the propensity not to use chemotherapy in reclassified low-risk patients exceeds 60%.

In probabilistic analyses, more than two thirds of simulations showed the recurrence score to improve QALYs and save costs. The upper 95th percentile of cost utility equaled $16 874.

Table 7. Sensitivity Analyses

Variables	Assumptions	QALYs Gained, y	Difference in Costs, $	Cost per QALY gained, $
Base case		8.6	–202,828	Cost saving
Probability of recurrence in 10 years				
If high risk (21.9%)				
Lower bound	Decrease by 50%	9.9	–258 891	Cost saving
Upper bound	Increase by 50%	6.2	–194 024	Cost saving
If low risk (7.8%)				
Lower bound	Decrease by 50%	7.2	–200 068	Cost saving
Upper bound	Increase by 50%	9.4	–204 337	Cost saving
Proportion of patients tested by RT-PCR who are low risk by NCCN criteria (7.9%)				
Lower bound	0%	7.4	–282 801	Cost saving
Upper bound	100%	23.1	725 166	31 529
Propensity to change treatment due to risk reclassification based on recurrence score result (100%)				
If high risk, lower bound	50%	5.2	86 168	17 234
If low risk, upper bound	50%	7.7	–212 919	Cost saving
RRR of recurrence with chemotherapy (15% if low risk and 45% if int/high risk)				
Lower bound	10% if low risk,	3.3	–246 287	Cost saving
Upper bound	30% if int/high risk	8.0	–157 573	Cost saving
Probability of death after recurrence, annual (40%)				
Lower bound	20%	9.3	–142 125	Cost saving
Upper bound	60%	8.5	–210 854	Cost saving
Probability of chemotherapy toxicity*				
Lower bound	Decrease all by 50%	8.6	–151 203	Cost saving
Upper bound	Increase all by 50%	8.6	–223 477	Cost saving
% of cancers HER2/neu+ (25%)				
Lower bound	20%	8.6	–200 864	Cost saving
Upper bound	30%	8.6	–205 321	Cost saving
Utility of no recurrence, lower bound (0.98)	0.90	8.8	–202 828	Cost saving
Utility of adjuvant chemotherapy				
Lower bound	0.20	15.0	–202 828	Cost saving
Upper bound	0.80	2.2	–202 828	Cost saving
Utilities after recurrence*				
Lower bound	Decrease all by 15%	8.5	–101 265	Cost saving
Upper bound	Increase all by 15%	8.7	–303 790	Cost saving
Cost of drugs for adjuvant chemotherapy*				
Lower bound	Decrease all by 15%	8.6	–101 865	Cost saving
Upper bound	Increase all by 15%	8.6	–303 790	Cost saving
Other chemotherapy costs*				
Lower bound	Decrease all by 15%	8.6	–213 618	Cost saving
Upper bound	Increase all by 15%	8.6	–192 037	Cost saving
Primary cancer surveillance if no distant recurrence, per year ($421)				
Lower bound	$200	8.6	–188 131	Cost saving
Upper bound	$1000	8.6	–241 333	Cost saving
Progressive metastatic disease, per year ($4680)				
Lower bound	$3500	8.6	–210 577	Cost saving
Upper bound	$6000	8.6	194 159	Cost saving
End-of-life ($30 000)				
Lower bound	$23 000	8.6	–214 631	Cost saving
Upper bound	$37 000	8.6	–191 024	Cost saving
Time horizon (50 y); lower bound	20 y	9.8	–126 530	Cost saving
Discount rate (3%)				
Lower bound	0%	6.5	–284 800	Cost saving
Upper bound	5%	9.3	–187 551	Cost saving

*See Tables 2 and 3.
DRFS indicates distant recurrence-free survival; ER+, estrogen-receptor–positive; LN–, lymph-node–negative; NCCN, National Comprehensive Cancer Network; OS, overall survival; QALY, quality-adjusted life years; RS, recurrence score; RRR, relative risk reduction; RT-PCR, reverse transcriptase-polymerase chain reaction.

DISCUSSION

Our study projects the benefits, costs, and cost effectiveness of a genomic test based on empirical evidence of its clinical effectiveness, and has 3 primary findings. First, reclassifying patients who were NCCN-defined as low risk to intermediate/high risk by the recurrence score was projected to increase overall survival, quality-adjusted survival, and costs. The average gain in OS per reclassified patient was estimated to be 1.86 years. Total costs were estimated to increase by about $25 000 ($12 190 to identify intermediate-/high-risk patients and at least $15 000 for chemotherapy, offset by savings of $2344 because of lower risk of recurrence). The cost utility of recurrence score testing for this cohort was $31 452 per QALY gained. Second, reclassifying NCCN-defined high-risk patients as low risk by the recurrence score was cost saving; the added $7073 testing to identify 1 reclassified patient was offset by the $15 000 savings for not using chemotherapy. Third, in a population of 100 patients with characteristics similar to those of the NSABP B-14 participants, more than 90% of whom were NCCN-defined as high risk, using the 21-gene RT-PCR assay was expected to improve quality-adjusted survival and save costs.

Our analyses applied efficacy and costs assumptions concerning patterns of prescribing chemotherapy based on physician surveys conducted in 2003. These analyses are important steps to calibrate the effects of chemotherapy on quality of life and to validate use of the methodology to evaluate the 21-gene RT-PCR assay.[52]

No threshold of cost effectiveness has been universally adopted as a standard that policymakers must use in deciding whether to adopt or fund new medical technologies.[53,54] Other factors influencing funding decisions include community and practioners' perceptions of medical necessity,[55] quality of evidence, disparities of care,[56] and impact of funding on overall budgets, especially when addressing competing organizational objectives. In 2000, Earle and colleagues summarized the literature on ranges of cost-effectiveness ratios for almost 90 assessments of cancer interventions.[38] They found a large range in cost-effectiveness ratios, with some cost-saving technologies, such as obtaining a biopsy from a 50-year-old man with elevated prostate-specific antigen levels,[57] to other technologies having cost-effectiveness ratios exceeding $1 million per QALY saved, such as immune globulin for chronic lymphocytic leukemia.[58] Sixty-four percent of cancer interventions had a cost-effectiveness ratio of $50 000 or less.[38] Commenting on thresholds of cost effectiveness in general, Ubel et al recently argued that technologies with cost-effectiveness ratios of less than $100 000 would represent reasonable public investments.[59] Arguing from a broad perspective of public investment in societal goods, such as health, education, environment, and defense, Garber and Phelps stated that interventions would be considered reasonable public investments if cost-effectiveness ratios were less than twice average annual income.[60] By any of these standards, the estimated cost effectiveness of this prospectively validated genomic assay—when appropriately used to improve classification of risk in patients with ESBC—is within the accepted range of other generally accepted healthcare technologies funded in the United States.

The commercial version of the assay has been available since early 2004, and more remains to be learned about its optimal use. Bast and Hortobagyi[61] recently highlighted several important questions about the assay that require further research prior to its widespread adoption in clinical practice, such as, how well does the recurrence score predict prognosis in women not receiving hormone therapy? and, does the assay predict response to chemotherapy? Studies have been completed[62] and are ongoing to assess the prognostic and predictive ability of the recurrence score—specifically, how the assay performs for patients with ER– or LN+ disease and whether the test can predict response to chemotherapy. Preliminary data suggest that the recurrence score has a positive correlation with the relative risk reduction of chemotherapy, a finding that would make the test even more useful: a high-risk score predicts greater benefit of chemotherapy and vice versa.[37,63]

Our study complements Bast and Hortobagyi's editorial by revealing other factors that are likely to influence the societal benefits and costs of the test. We found that these outcomes were highly influenced by (1) how patients and physicians interpret and use the results of the assay and (2) whether the assay will be used in all patients with LN–, ER+ ESBC or restricted to a subset of patients. For example, a hypothetical scenario in which use of this assay could be inefficient is one in which patients reclassified from NCCN-defined high risk to low risk by the recurrence score were to rarely change their decision to receive chemotherapy. As shown here, it will be important to follow trends of testing and treatment patterns using available clinical databases and registries, and update economic analyses in light of relevant clinical evidence and data on evolving practice patterns. Moreover, because of the small percentage of patients who were classified by NCCN as low risk, additional evidence from other studies is needed on DRFS among such women who are reclassified to high risk by the

recurrence score. Our sensitivity analyses captured the uncertainty in this variable.

Newer agents being developed for adjuvant and neoadjuvant settings, such as extended use of aromatase inhibitors, use of trastuzumab, and dose-dense regimens, appear likely to further increase the cost of chemotherapy. Our sensitivity analyses show that as costs associated with chemotherapy increase, so does the cost effectiveness of the test, further highlighting the need for more predictive approaches than are currently available to classify recurrence risk. Also, the 21-gene RT-PCR assay is a first-generation test. The field of molecular diagnostics is progressing rapidly with development of second-generation assays that will include more genes and that may further improve the prognostic and predictive accuracy of the assay. For now, the assay has been validated in patients with LN–, ER+ ESBC. This cohort was important to study initially because, with enhanced screening, more patients are being diagnosed with ESBC. Implications of the assay for patients with LN+ and ER– cancers has yet to be determined.

We deliberately omitted a number of factors that may further influence the clinical utility and economics of the assay. For example, we did not include an adjustment in quality of life to account for the effect the test may have on decision making for patients and physicians. Patients have reported a strong desire for information to facilitate decision making and to build confidence in their decisions.[63] How the assay might affect patients' attitudes about their decisions has not been assessed prospectively, but should be monitored as use of the assay increases. Other questions worth pursuing include: Do patients feel the assay helped them to better understand the risks and benefits of chemotherapy? Does the assay result influence their decision to undergo chemotherapy? Do they feel more or less confident about their decision to receive or forego chemotherapy because of the assay result?

The assay also may have implications for other aspects of management of ESBC, such as method and interpretation of lymph node staging, interpretation of immunohistochemistry of lymph nodes, and intensity of posttreatment cancer surveillance. With the databases currently available, assessing such potential impacts is difficult. As genomic assays like the one studied here become more widely available, prospective studies will provide information on how they influence various aspects of quality of care, patient safety, and costs.

Experts widely perceive that adherence to guidelines is significantly less than 100%.[10,20,21,64,65] While not assessed here, a low score on the recurrence score may conceivably boost patients' and physicians' confidence in foregoing chemotherapy when NCCN criteria also define patients as having low risk of recurrence.

In summary, the recurrence score for predicting risk of distant recurrence from LN–, ER+ ESBC was shown prospectively to more accurately forecast outcomes than existing guidelines. The recurrence score, derived from a 21-gene RT-PCR assay—one of the first commercially available genomic assays—shows potential to align adjuvant chemotherapy decisions more closely with risk, thereby improving quality-adjusted survival and providing more efficient use of resources for managing breast cancer. The results of this analysis should help in developing guidelines to assure optimal and efficient use of the assay.

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