

Impact of a 21-Gene RT-PCR Assay on Treatment Decisions in Early-Stage Breast Cancer

An Economic Analysis Based on Prognostic and Predictive Validation Studies

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BACKGROUND. The prognostic accuracy for distant recurrence-free survival using a 21-gene reverse-transcriptase polymerase chain reaction (RT-PCR) assay underwent validation in 668 lymph node-negative, estrogen receptor-positive women with early-stage breast cancer receiving tamoxifen on National Surgical Adjuvant Breast Program (NSABP) B-14. The predictive accuracy for treatment efficacy also underwent validation in 651 patients randomized on NSABP B-20 and 645 patients on NSABP B-14.

METHODS. Patients were classified as high (recurrence score [RS] ≥ 31), intermediate (RS 18–30), or low (RS < 18) risk for distant recurrence at 10 years. Cost-effectiveness ratios were estimated for RS-guided treatment compared with either tamoxifen alone or the combined chemotherapy and tamoxifen.

RESULTS. Distant recurrence was reported in RS low-risk, intermediate-risk, and high-risk patients at 10 years in 3.7%, 17.8%, and 38.3% receiving tamoxifen alone and 5.0%, 10.1%, and 11.1% receiving the chemotherapy and tamoxifen. RS-guided therapy is associated with a gain in individual life expectancy of 2.2 years compared with tamoxifen alone, whereas it is associated with similar life expectancy to that seen with the chemotherapy and tamoxifen strategy. RS-guided therapy is estimated to provide a net cost savings of \$2256 compared with chemotherapy and tamoxifen with an incremental cost-effectiveness ratio of \$1944 per life year saved compared with tamoxifen alone.

CONCLUSIONS. Treatment decisions based on RS-guided therapy compared with tamoxifen alone are associated with greater efficacy with acceptable cost-effectiveness ratios, and associated with similar efficacy and lower cost compared with chemotherapy and tamoxifen for patients with lymph node-negative, estrogen receptor-positive early-stage breast cancer. *Cancer* 2007;109:1011–8. © 2007 American Cancer Society.

KEYWORDS: breast cancer, 21-gene RT-PCR, lymph node-negative, estrogen receptor-positive, tamoxifen, microarray, adjuvant chemotherapy, economic analysis, costs.

More than 200,000 women are diagnosed with invasive breast cancer in the US annually, with approximately 40,000 dying from the disease, with nearly half of these women presenting with lymph node-negative, hormone receptor-positive disease.¹ The decision to treat early-stage breast cancer (ESBC) with adjuvant hormonal therapy and/or chemotherapy is based on several clinical and pathological criteria. Current guidelines for the management of patients with ESBC recommend adjuvant chemotherapy and endocrine therapy for the majority of women with lymph node-negative, hormone receptor-positive ESBC.^{2,3} Unfortunately, systemic chemotherapy is associated with considerable immediate morbidity and

cost along with increasing evidence for significant delayed toxicities such as neurocognitive dysfunction and secondary malignancies.

Many patients with lymph node-negative, hormone receptor-positive ESBC do not experience distant recurrences or death from breast cancer even in the absence of adjuvant chemotherapy. At the same time, randomized controlled trials have demonstrated that some patients develop distant recurrence despite receiving adjuvant chemotherapy.⁴ Due in large part to the limited ability of clinical criteria to accurately assess an individual's risk, many patients continue to be overtreated or undertreated. Interest has recently developed in the possible role of gene expression profiles and other molecular techniques in more accurately assessing the risk of recurrence and the impact of treatment to guide clinical decisions on adjuvant therapy.⁵

A gene expression profile assay has been developed based on reverse-transcriptase polymerase chain reaction (RT-PCR) methods that permit quantification of gene expression in fixed paraffin-embedded tissue.⁶ Candidate genes consisted of 250 cancer-related genes gathered from the cancer literature, genomic databases, and microarray data.⁷⁻¹⁰ A 21-gene expression signature including 16 functional and 5 references genes was found to provide excellent RT-PCR performance. Prognostic information was obtained on 447 women with ESBC including 233 from the National Surgical Adjuvant Breast Program (NSABP) Study B-20 in whom archived tissue was available.¹¹ A recurrence score (RS; *Oncotype DX*) ranging from 0-100 was derived from each patient's gene expression results using a proprietary formula. This 21-gene signature has been independently validated as a prognostic indicator of distant recurrence-free survival in 668 evaluable patients in node-negative, receptor-positive ESBC receiving tamoxifen on the NSABP B-14 study.¹²⁻¹⁵ Multivariate analysis demonstrated this assay to be a significant independent prognostic factor for distant recurrence after adjustment for age and tumor size with an adjusted hazard ratio of 3.21 (95% confidence interval [CI]: 2.23, 4.61; $P < .00001$).¹¹

A previous economic analysis based on the initial validation of the prognostic capability of the assay has been reported.¹⁶ A cost-utility analysis was conducted using the RS in patients classified as having a low or high risk of distant recurrence based on National Comprehensive Cancer Network (NCCN) clinical guidelines. The analysis considered survival, quality of life, and costs from a societal perspective. At baseline values, the RS applied to 100 potential patients predicted an increase quality-adjusted survival by 8.6 years while reducing overall costs by

\$202,828. The RS was more accurate than NCCN guidelines as an indicator of prognosis for lymph node-negative, estrogen receptor-positive ESBC and was cost effective.¹⁶ The predictive accuracy of the 21-gene signature has recently been validated based on the observed impact of chemotherapy and tamoxifen on distant recurrence-free survival (DRFS) among 651 patients on NSABP B-20 and 645 patients on NSABP B-14.¹⁷ The study reported here incorporates the extended validation results into an economic model of the 21-gene expression signature to guide the use of adjuvant chemotherapy and hormonal therapy in patients with lymph node-negative, estrogen receptor-positive ESBC.

MATERIALS AND METHODS

Risk Assessment

As noted above, the original validation study of prognostic accuracy for the 21-gene expression signature was based on women with lymph node-negative, estrogen receptor-positive ESBC treated with tamoxifen on NSABP B-14. Of the 2617 eligible women, 688 were evaluable based on availability of the original tumor block and adequate tumor to provide RNA for RT-PCR analysis.¹¹ The predictive accuracy for DRFS based on response to chemotherapy and tamoxifen has also undergone validation in 651 patients randomized on NSABP B-20 and 645 patients on NSABP B-14.¹⁷ An RS was generated as a continuous measure by fitting a time-varying piece-wise log-hazard ratio model to the data, whereas the 10-year distant recurrence rate was estimated by a Breslow-type estimator as previously described.¹⁸ Women with node-negative, receptor-positive ESBC were classified as high (RS \geq 31), intermediate (RS 18-30), or low (RS $<$ 18) risk of distant recurrence at 10 years (Fig. 1).¹¹

Outcome Measures

The clinical impact of different treatment strategies was assessed by estimating the gain in life expectancy or life years saved derived from NSABP B-20 and B-14. The impact of treatment strategies on health-related quality of life was based on a time trade-off method where patients are asked to state the maximum number of years of their actual life expectancy in the diseased state that they would be willing to give up for time in full health. This method is based on the premise that many patients would be willing to give up some length of survival for a higher quality of survival if that was a viable option. Clinical outcomes were expressed in the form of quality-adjusted life years (QALYs) by taking the product of the actual life expectancy and the patient utility.

Data on costs of cancer care were obtained from the Centers for Medicare and Medicaid Services as well as published literature and are described else-

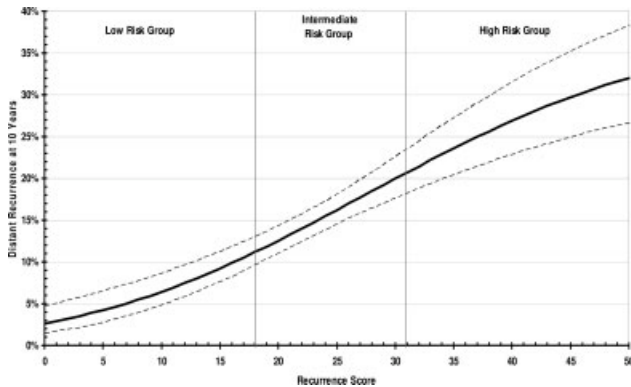


FIGURE 1. NSABP B-14 prospective clinical validation study with recurrence score as a continuous predictor. Data are fitted by a time-varying, piece-wise, log-hazard ratio model (Gray, *JASA*. 1992), and the 10-year distant recurrence rate was estimated by a Breslow-type estimator (Valenta and Weissfeld, *Stat Med*. 2002). Reprinted with permission of the Massachusetts Medical Society. Copyright ©2004 Massachusetts Medical Society. All rights reserved. Originally published in Paik et al. *N Engl J Med*. 2004;351:2817–2826.

where.^{16,19} Chemotherapy costs were based on reported Average Wholesale Price and include only drug costs. Other treatment-related direct and indirect costs were not considered, eg, costs of administration, testing, transportation, etc. Utility estimates for the quality of life impact of adjuvant breast cancer chemotherapy were derived from the literature as described above.^{20,21} Costs not considered in this analysis include both additional direct costs associated with drug administration, professional fees, and laboratory testing along with indirect costs such as transportation and loss of productivity costs and patient out-of-pocket expenses.

Cost Effectiveness and Cost Utility

A clinical decision model was developed comparing clinical, economic, and quality of life outcomes for 3 adjuvant treatment strategies: 1) tamoxifen alone, 2) chemotherapy followed by tamoxifen, or 3) RS-guided therapy based on the results of the 21-gene RT-PCR assay. The RS-guided strategy employs tamoxifen for low-risk patients and chemotherapy and tamoxifen for intermediate- and high-risk patients. Table 1 presents baseline probability and cost assump-

TABLE 1
Baseline Values Subjected to Sensitivity Analyses

Group	Group	Baseline value	Range	Distribution type	Source
10-Year distant recurrence-free survival					
Low risk	Tamoxifen	96.3			
	Chemotherapy+tamoxifen	95.0			
	RS-guided therapy	96.3			
Intermediate risk	Tamoxifen	82.2			
	Chemotherapy+tamoxifen	89.9	—	Binomial	Paik et al. ¹¹
	RS-guided therapy	89.9			
High risk	Tamoxifen	61.7			
	Chemotherapy+tamoxifen	88.9			
	RS-guided therapy	88.9			
Proportions					
Low risk patients		0.54			
Intermediate risk patients		0.21	—	—	Paik et al. ¹¹
High risk patients		0.25			
Direct costs (\$)					
	Adjuvant chemotherapy	10,000	500–25,000	Normal, SD 2500	CMS Oestreicher et al. ¹⁹
	Surveillance without recurrence	5,000	500–20,000	Normal, SD 1000	CMS Oestreicher et al. ¹⁹
	OncotypeDx assay	3,460	—	—	Genomic health
	Treatment of recurrence	50,000	10,000–150,000	Normal, SD 20,000	CMS Oestreicher et al. ¹⁹
Time					
	Healthy life expectancy, y	20	5–30	—	NCHS
	Annual mortality rate following recurrence	0.347	—	—	Paik et al. ¹¹
Quality of life	Utility with chemotherapy	1.0	0.5–1.0	—	Earle et al. ²⁰

SD indicates standard deviation; GH, genomic health [www.genomichealth.com]; CMS, Center for Medicine and Medicaid services [www.cms.hhs.gov]; NCHS, National Center for Health Statistics [www.cdc.gov/nchs/].

TABLE 2
Cost-Effectiveness of 21-Gene RT-PCR Assay

Treatment strategy	Cost (\$) per life year saved (LYS)				
	Cost	LYS	ΔCost	ΔLYS	ΔC/E LYS
Tamoxifen	\$11,890	26.07	—	—	—
RS-guided	\$16,162	28.27	\$4,272	2.197	\$1944
Chemotherapy and Tamoxifen	\$18,418	28.10	\$6,527	1.928	\$3385

C/E indicates cost effectiveness; RT-PCR, reverse-transcription polymerase chain reaction. Under baseline conditions; no quality of life adjustment.

tions. Treatment strategies were compared in the framework of cost-effectiveness and cost-utility analyses providing summary outcome measures reflecting additional cost of 1 strategy over another (marginal cost) and the additional clinical benefit (marginal efficacy) or quality-adjusted clinical benefit (marginal utility). The balance between cost and benefit was expressed in terms of cost-effectiveness (C/E) and cost-utility (C/U) ratios of the marginal cost and the marginal effectiveness representing the added cost per life year or QALY saved.²²⁻²⁴ Incremental costs (\$), life years, QALYs, as well as C/E and C/U ratios were estimated for each treatment strategy.

Monte Carlo Simulation

Monte Carlo simulation was conducted for DRFS and estimated costs based on available distributions. Sampling distributions and summary estimates of cost, efficacy, and variance were based on 1000 replicates.

RESULTS

Risk Stratification

Of the 651 patients on NSABP B20 with corresponding gene expression assays, 64 (9.83%) developed distant recurrence including 31 (13.66%) randomized to tamoxifen and 33 (7.78%) receiving chemotherapy and tamoxifen. Distant recurrence was observed within 10 years in 3.2%, 9.1%, and 39.5% of RS low-risk, intermediate-risk, and high-risk patients, respectively, receiving tamoxifen alone and in 4.4%, 10.9%, and 11.9% in those receiving chemotherapy and tamoxifen. No significant difference in life expectancy at 10 years was seen between the RS-guided therapy and the combined chemotherapy and tamoxifen strategies, whereas RS-guided therapy is associated with a gain in individual life expectancy of 2.2 years compared with tamoxifen alone.

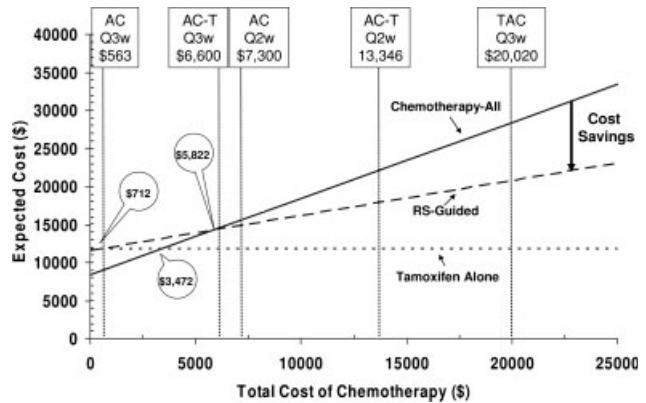


FIGURE 2. Graphical display of the expected costs of treatment by strategy for increasing costs associated with chemotherapy. The comparative drug costs estimated for 5 commonly used adjuvant chemotherapy regimens are indicated including: 1) doxorubicin and cyclophosphamide (AC) every 3 weeks × 4 cycles; 2) AC every 2 weeks × 4 cycles with colony-stimulating factor (CSF) support; 3) AC followed by paclitaxel (AC-T) every 3 weeks × 8 cycles; 4) AC-T every 2 weeks × 8 cycles with CSF support; and 5) docetaxel, doxorubicin, and cyclophosphamide (TAC) every 3 weeks × 6 cycles with CSF support.

Expected Costs

Under baseline cost assumptions, the lowest expected overall cost is associated with treatment with tamoxifen alone, whereas the greatest expected cost is that associated with the chemotherapy and tamoxifen strategy (Table 2). The expected costs of each strategy increase as the cost of treating distant recurrence increases. Above a cost of treating recurrence of \$100,759, RS-guided therapy provides a net cost savings compared with other strategies and is always cost-saving compared with the chemotherapy and tamoxifen strategy. Tamoxifen is associated with lowest costs for all reasonable follow-up cost assumptions among those not recurring, whereas RS-guided therapy is always associated with lower costs than a chemotherapy and tamoxifen strategy.

The expected costs associated with both the chemotherapy and tamoxifen and the RS-guided therapy strategies increase as the direct cost of chemotherapy increases, but they do so at different rates. As shown in Figure 2, the expected costs favor the RS-guided therapy strategy over the chemotherapy and tamoxifen strategies, for total chemotherapy costs exceed \$5822. The estimated costs associated with 5 commonly used adjuvant chemotherapy regimens are indicated including: 1) doxorubicin and cyclophosphamide (AC) every 3 weeks × 4 cycles; 2) AC every 2 weeks × 4 cycles with colony-stimulating factor (CSF) support; 3) AC followed by paclitaxel (AC-T) every 3 weeks × 8 cycles; 4) AC-T every 2

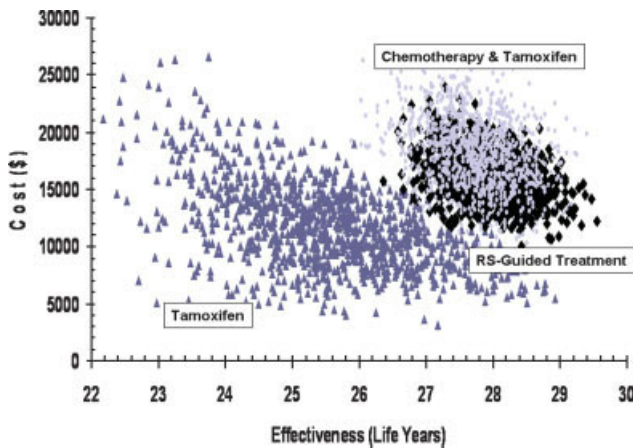


FIGURE 3. Cost-effectiveness scatterplot for 3 therapeutic strategies considered. Treatment effectiveness in life years saved is represented by the horizontal axis and the costs (\$) on the vertical axis.

weeks \times 8 cycles with CSF support; and 5) docetaxel, doxorubicin, and cyclophosphamide (TAC) every 3 weeks \times 6 with CSF support. Whereas every 3-week doxorubicin and cyclophosphamide without myeloid growth factor support is associated with a lower cost, most of the commonly used adjuvant breast cancer regimens are associated with costs that favor their targeted use based on the 21-gene expression signature. A net cost savings is estimated for RS-guided therapy for: AC-T Q3 weeks (\$458); AC Q2 weeks (\$946); AC-T Q2 weeks (\$5159), and TAC Q3 weeks (\$9810).

Incremental Cost-Effectiveness

The expected incremental costs associated with the RS-guided therapy and chemotherapy and tamoxifen strategies are \$4272 and \$6527, respectively, compared with tamoxifen alone (Table 2). The incremental cost-effectiveness ratio compared with tamoxifen alone favors the RS-guided therapy strategy (\$1944/life year saved) over the chemotherapy and tamoxifen approach (\$3385/life year saved). Incremental life years saved for the RS-guided therapy compared with tamoxifen alone increases as healthy life expectancy increases, whereas the cost effectiveness decreases from \$41,433/life year saved at a healthy life expectancy of 5 years to \$1101/life year saved with a life expectancy of 40 years to chemotherapy and tamoxifen with varying healthy life expectancy.

Cost Utility

The baseline assumptions indicated in Table 1 reflect no adjustment for the impact of chemotherapy on quality-of-life. Such adjustments have the anticipated effect on the estimated QALYs and, therefore, the cost utility or cost per QALY gained. Expected QALYs

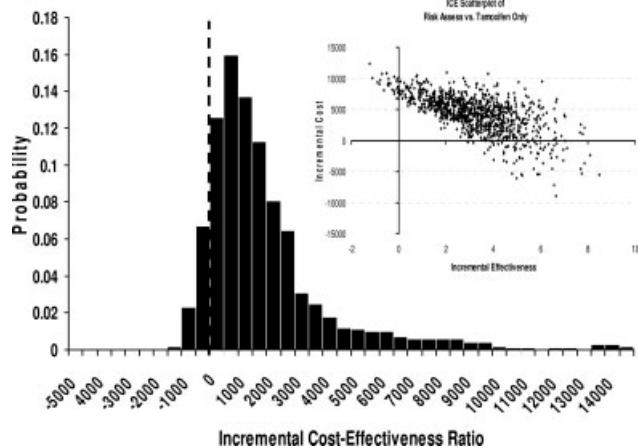


FIGURE 4. Distribution of incremental cost-effectiveness ratios derived from Monte Carlo simulation ($N = 1000$) for the comparison of RS-guided therapy with tamoxifen alone. Inset presents a scatter plot of the incremental cost (\$) and incremental effectiveness (years).

were found to favor the RS-guided therapy strategy over chemotherapy and tamoxifen for all values of health utility, with increasing incremental QALY as the impact of chemotherapy on measured utility increased. The utility associated with chemotherapy has no impact on the expected QALYs associated with the tamoxifen-alone strategy. Greater expected QALYs compared with tamoxifen alone are seen for RS-guided therapy until the utility associated with chemotherapy falls below 0.80. At a utility of 0.90 associated with adjuvant chemotherapy, RS-guided therapy is associated with a gain of 0.97 QALYs and a cost utility of \$4432/QALY compared with tamoxifen alone and a gain in 1.71 QALYs compared with the chemotherapy and tamoxifen combination despite a net cost savings.

Monte Carlo Simulation

Monte Carlo simulation was conducted as described above. Mean and median incremental cost-effectiveness ratios were \$2769/life year saved and \$1784/life year saved, respectively, for RS-guided therapy compared with tamoxifen alone. As shown in the cost-effectiveness scatterplot (Fig. 3), the RS-guided therapy and the chemotherapy strategies are associated with quite separate distributions of costs and effectiveness compared with that associated with tamoxifen alone. Assessment of the incremental cost-effectiveness ratios demonstrate that the relation between RS-guided therapy and tamoxifen alone is primarily that of an increase in life years saved, albeit with a small increase in cost resulting in cost-effectiveness ratios with a very high probability of falling below \$50,000/life year saved (Fig. 4). An

assessment of the incremental cost-effectiveness ratios for the relation between RS-guided therapy and the chemotherapy and tamoxifen strategy demonstrates that the RS-guided therapy reduces the estimated cost with an actual reduction in cost in 70% of replicates in Monte Carlo analysis and an overall benefit in terms of life expectancy. In a willingness-to-pay (WTP) analysis (data not shown), under baseline conditions and a WTP value = 0, the tamoxifen-alone arm is favored by virtue of being the least costly option. The RS-guided therapy option becomes equally favored at a WTP of \$7500/life year saved. The chemotherapy and tamoxifen strategy is equally favored compared with tamoxifen at a WTP of \$13,000, whereas the RS-guided therapy remains the favored option approximately 70% of the time when the WTP exceeds \$15,000/life year saved.

DISCUSSION

Treatment decisions based on the RS-guided therapy compared with tamoxifen alone are associated with greater efficacy, with cost-effectiveness ratios well within accepted ranges for technology adoption, whereas they are associated with similar efficacy and substantially lower toxicity and cost compared with chemotherapy and tamoxifen for all patients. Decisions on the adjuvant treatment of women with ESBC are often based on patient age or menopausal status as well as clinical and pathological factors associated with limited prognostic accuracy.^{25,26} Multiple large, randomized, controlled trials and meta-analyses of those trials have demonstrated the efficacy of adjuvant systemic therapy in ESBC. Nevertheless, systemic chemotherapy is associated with short-term as well as long-term toxicities of considerable concern. As a result, many patients receive potentially toxic adjuvant chemotherapy who are already disease-free, whereas some do not receive potentially curative adjuvant therapy who might have benefited. Current clinical guidelines encourage the use of adjuvant chemotherapy in addition to hormonal therapy in all but the lowest risk categories of lymph node-negative, estrogen receptor-positive women with ESBC.^{2,3} The 21-gene expression signature RS for distant disease recurrence was initially validated in 668 evaluable lymph node-negative, estrogen receptor-positive ESBC patients receiving tamoxifen on NSABP B-14.¹¹ More recently, the predictive accuracy of the assay has also been validation-based on the response to chemotherapy and tamoxifen in 651 patients on NSABP B-20 and 645 patients on NSABP B-14.¹⁷ The study reported here was undertaken to further evaluate the economic

impact of the 21-gene signature when used to guide common clinical decisions concerning the use of adjuvant chemotherapy and hormonal therapy in patients with lymph node-negative, estrogen receptor-positive ESBC. The economic impact of the gene expression profile signature to guide the type of adjuvant systemic therapy was compared with the strategy of tamoxifen alone or chemotherapy and tamoxifen.

Under baseline assumptions, the lowest expected cost was found to be associated with tamoxifen alone, whereas the RS-guided therapy strategy was associated with lower expected costs than the chemotherapy strategy. The estimated incremental cost with RS-guided therapy and chemotherapy compared with tamoxifen alone was \$4272 and \$6527, respectively. An estimated average cost savings of more than \$2000 was estimated for RS-guided treatment. The estimated incremental cost per life year saved compared with tamoxifen alone favored RS-guided therapy over the chemotherapy strategy, with a cost saving of over \$1000 per life year saved with RS-guided therapy. The RS-guided therapy strategy was found to be more costly for low-cost chemotherapy regimens not requiring additional supportive care, whereas a net cost savings between \$500 and \$10,000 is estimated with RS-guided therapy for other commonly used adjuvant chemotherapy regimens. The estimated cost savings provided here for RS-guided therapy are probably underestimates, as they do not consider other direct costs associated with adjuvant chemotherapy including drug administration, professional fees, laboratory testing and the costs of complications. In addition, the model does not consider indirect costs such as those associated with transportation and loss of productivity costs as well as out-of-pocket expenses. Therefore, it is likely that additional savings from a societal perspective would be associated with the RS-guided therapy strategy.

Several studies have addressed the potential impact of cancer chemotherapy on patient quality of life.²⁷⁻³¹ Whereas no quality of life adjustment was considered under baseline conditions, the greater the impact of chemotherapy on quality of life, the greater the incremental cost utility favoring RS-guided therapy compared with systemic chemotherapy. Likewise, RS-guided therapy was associated with superior cost utility compared with tamoxifen alone for chemotherapy utility exceeding 80%.

Despite the favorable clinical and economic results for the 21-gene assay presented here, it is clear that more work is needed to develop assays with both greater accuracy as well as broader clinical application. As with this assay, careful and compre-

hensive validation of assays with potential use in estimating disease prognosis and treatment response in women with ESBC is needed.^{32–35} A recent review of 17 studies of gene expression assays with validation based on recurrence-free survival in women with ESBC in a broad range of potential clinical settings demonstrates wide variation in test accuracy.³⁶ Assay performance measures including sensitivity and specificity varied widely across studies. Of potential interest for investigators in future studies is the observed significant correlation between the number of genes in the assay and test performance as reflected in the diagnostic odds ratio. As gene expression assays and other biomarkers improve in prognostic and predictive accuracy, further increases in the clinical benefit and cost effectiveness of these tools should be achieved.

In summary, RS-guided therapy applied to lymph node-negative, estrogen receptor-positive ESBC is associated with lower expected cost per life year or QALY gained compared with empiric chemotherapy across all reasonable model assumptions. The use of the gene expression assay in targeting systemic chemotherapy and hormonal therapy toward ESBC patients at greatest risk and most likely to benefit appears to have the potential to provide a net cost savings or to prolong survival along with acceptable cost-effectiveness ratios compared with other commonly used adjuvant treatment strategies. Nevertheless, further evaluation of the clinical utility of gene expression profile signatures in women with ESBC is needed. A large Phase III trial (TAILORx) sponsored by the National Cancer Institute is currently being conducted assigning lymph node-negative, estrogen receptor-positive women with breast cancer hormonal therapy if $RS < 11$, combination of adjuvant chemotherapy and hormonal therapy if $RS > 25$, and randomizing patients with $RS 11–15$ to either hormonal therapy or combination chemotherapy and hormonal therapy. This study will hopefully further define the potential role of the 21-gene expression assay in women with intermediate RS results.

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