VOLUME 36 · NUMBER 6 · FEBRUARY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cost Effectiveness of Gene Expression Profile Testing in Community Practice

Young Chandler, Clyde B. Schechter, Jinani Jayasekera, Aimee Near, Suzanne C. O'Neill, Claudine Isaacs, Charles E. Phelps, G. Thomas Ray, Tracy A. Lieu, Scott Ramsey, and Jeanne S. Mandelblatt

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on January 8, 2018.

Corresponding author: Young Chandler, PhD, Lombardi Comprehensive Cancer Center, 3300 Whitehaven St, Northwest, Ste 4100, Washington, DC 20007; e-mail, yc377@georgetown.edu.

0732-183X/18/3606w-554w/$20.00

ABSTRACT

Purpose

Gene expression profile (GEP) testing can support chemotherapy decision making for patients with early-stage, estrogen receptor–positive, human epidermal growth factor 2–negative breast cancers. This study evaluated the cost effectiveness of one GEP test, Onco*type* DX (Genomic Health, Redwood City, CA), in community practice with test-eligible patients age 40 to 79 years.

Methods

A simulation model compared 25-year societal incremental costs and quality-adjusted life-years (QALYs) of community Onco*type* DX use from 2005 to 2012 versus usual care in the pretesting era (2000 to 2004). Inputs included Onco*type* DX and chemotherapy data from an integrated health care system and national and published data on Onco*type* DX accuracy, chemotherapy effectiveness, utilities, survival and recurrence, and Medicare and patient costs. Sensitivity analyses varied individual parameters; results were also estimated for ideal conditions (ie, 100% testing and adherence to test-suggested treatment, perfect test accuracy, considering test effects on reassurance or worry, and lowest costs).

Results

Twenty-four percent of test-eligible patients had Onco*type* DX testing. Testing was higher in younger patients and patients with stage I disease (*v* stage IIA), and 75.3% and 10.2% of patients with high and low recurrence risk scores received chemotherapy, respectively. The cost-effectiveness ratio for testing (*v* usual care) was $188,125 per QALY. Considering test effects on worry versus reassurance decreased the cost-effectiveness ratio to $58,431 per QALY. With perfect test accuracy, the cost-effectiveness ratio was $28,947 per QALY, and under ideal conditions, it was $39,496 per QALY.

Conclusion

GEP testing is likely to have a high cost-effectiveness ratio on the basis of community practice patterns. However, realistic variations in assumptions about key variables could result in GEP testing having cost-effectiveness ratios in the range of other accepted interventions. The differences in cost-effectiveness ratios on the basis of community versus ideal conditions underscore the importance of considering real-world implementation when assessing the new technology.

J Clin Oncol 36:554-562. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Gene expression profile (GEP) tests, such as Onco*type* DX (Genomic Health, Redwood City, CA), have been recommended for use to support treatment decision making for patients with early-stage, node-negative, estrogen receptor (ER)–positive, human epidermal growth factor 2 (HER2)–negative cancers.[1-3] The primary goal of GEP testing is to identify patients at high recurrence risk who will benefit from chemotherapy, while allowing patients with a low recurrence risk to forego chemotherapy, potentially offsetting the test costs with savings from reductions in chemotherapy use.

To date, use of GEP testing in community practice remains low, ranging from 22% to 42% of test-eligible patients.[4-9] Moreover, chemotherapy use is sometimes discordant with test results, with 17% to 26% of patients with high recurrence risk scores not receiving chemotherapy and 8% of patients with low recurrence risk scores receiving chemotherapy.[10]

Prior economic analyses of GEP evaluated hypothetical cohorts under ideal conditions and

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.74.5034

DOI: https://doi.org/10.1200/JCO.2017.74.5034

concluded that it had low costs relative to its benefits.[11-17] However, given the divergence of community testing and chemotherapy use from the ideal, it is possible that the expected clinical and economic benefits of GEP are not being fully realized. In this study, we conducted an analysis of the likely cost effectiveness of Oncotype DX testing on the basis of community practice patterns.

METHODS

We constructed a discrete-time state transition simulation model to estimate the likely incremental costs per quality-adjusted life-year (QALY) of community use of Oncotype DX testing versus usual care from a societal perspective. The Georgetown University Oncology and Kaiser Permanente Northern California (KPNC) institutional review boards approved the research.

Intervention and Patients

We selected Oncotype DX because it is the most commonly used GEP test in the United States[10] and the primary focus of prior economic analyses.[11-17] The population included test-eligible patients age 40 to 79 years diagnosed with stage I or IIA, ER-positive, HER2-negative breast cancer between 2000 and 2012. Costs and effects for patients diagnosed from 2000 to 2004 (ie, pre–Oncotype DX period, usual care) were compared with those among patients diagnosed from 2005 to 2012 (ie, period when Oncotype DX testing was used in community practice).

Model Overview

The model was developed using TreeAge Pro 2015 (TreeAge Software, Williamstown, MA). The model captured a 25-year time horizon from diagnosis because the median age of diagnosis is > 60 years[18] and almost all distant recurrences (and deaths from recurrences) occur within 25 years of diagnosis.[19] Events (eg, chemotherapy use or toxicity) were tallied at 1-year transition intervals. The model decision pathways and health states are summarized in Figures 1A and 1B, respectively.

Briefly, the model began with the generation of simulated patients with breast cancer by age and stage on the basis of national incidence rates. In the usual care scenario, patients could receive chemotherapy or not on the basis of their age and stage. In the Oncotype DX testing period, patients were tested or not, and received chemotherapy on the basis of age, stage, and test use and results. If recurrence occurred, it was assumed to progress to breast cancer death within 25 years, unless death occurred earlier as a result

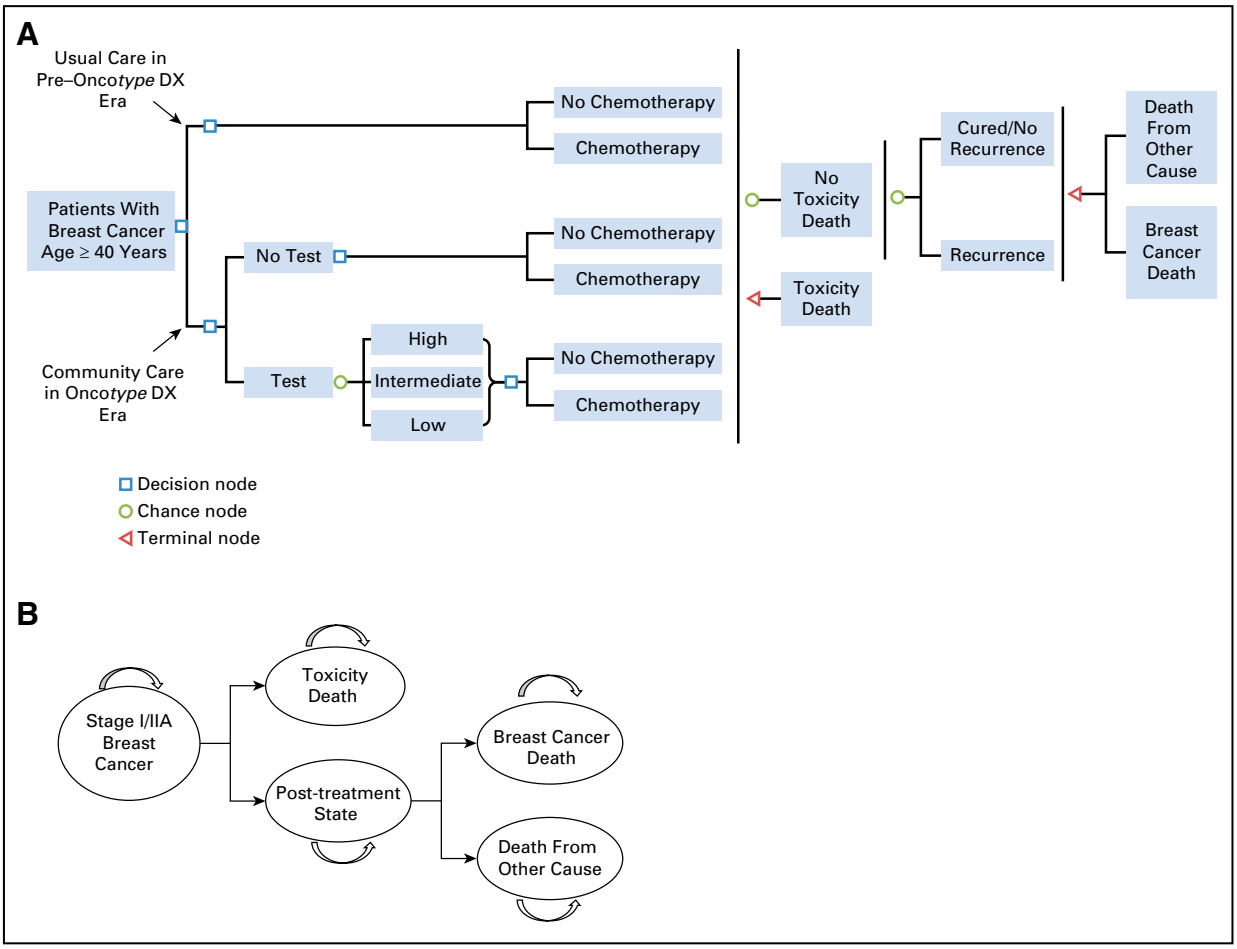

Fig 1. Decision tree and state transitions for patients with stage I or IIA, node-negative, estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. (A) Simulation model schema. The model was developed to compare cost effectiveness of community practice with use of Oncotype DX test versus usual care without the test. The community practice arm included observed testing and chemotherapy use in 2005 to 2012. The usual care arm included chemotherapy use patterns in the pre–Oncotype DX era (2000 to 2005). Testing probabilities were conditional on age and stage. The test results affected the probability of chemotherapy use. (B) State transition. All simulated patients were newly diagnosed with ER-positive, HER2-negative, node-negative, stage I or IIA breast cancer. If death from chemotherapy toxicity did not happen at initial treatment, all simulated patients transitioned to the post-treatment state until breast cancer death (if recurrence occurred) or death from other cause (if no recurrence occurred or death from other cause occurred before recurrence). Patients without distant recurrence only died of non–breast cancer causes or chemotherapy toxicity. Patients remain in the same state until the time of a transition event.

of chemotherapy toxicity or other causes. Without recurrence, patients died of other causes, and if chemotherapy was received, it did not provide benefit but could have resulted in toxicity.

Tracking variables built into the model were used to tally starting age, current age, recurrence status, testing status, test result, chemotherapy use, toxicity grade, and cause of death. These tracking variables were used in postprocessing analyses using SAS 9.4 (SAS Institute, Cary, NC), including calculation of life-years for each simulated patient, application of utility weights, cost allocation to each event, and discounting of costs and effects.

Input Parameters

Model inputs used to estimate costs and effects were derived from national data, published research, and KPNC electronic records linking registry data, treatment, and GEP testing (Table 1). Incidence rates were based on SEER data from 2000 to 2012.[21] Oncotype DX testing and chemotherapy use rates were based on age- and stage-specific use at KPNC.[8] The marginal distribution of risk score categories and the probability of recurrence conditional on each risk score category were based on published data.[3] Using Bayes' theorem, these data were used to calculate the probability of having each risk score category conditional on whether or not recurrence occurred, as a measure of the test accuracy.

The underlying age- and stage-specific 25-year breast cancer survival in the absence of treatment of ER-positive, HER2-negative, stage I and IIA cancers was based on prior Cancer Intervention and Surveillance Modeling Network analyses.[22,23] This overall survival was partitioned into survival among those who experienced distant recurrence and those who did not and was used to calculate annual risk of breast cancer death given recurrence status in the absence of any adjuvant treatment.

To isolate the effects of Oncotype DX on chemotherapy-related outcomes, we assumed that 100% of patients received hormonal therapy and that adherence was independent of Oncotype DX testing. Treatment with hormonal therapy alone or hormonal therapy and chemotherapy reduced the risk of death among those destined to have distant recurrences but had no effect on breast cancer mortality among those who would never experience recurrence. Treatment effects were based on the most recent meta-analysis from the Early Breast Cancer Collaborative Trialists' Group.[29] The probability of experiencing chemotherapy toxicity and toxicity grade were based on published trials.[24-28] Non–breast cancer mortality was based on US data.[30]

Survival was weighted by utility values for each health state to estimate QALYs. Utilities were based on female population age-specific values from the EQ-5D reported on the Medical Expenditure Panel Survey.[31,32] Among those who received chemotherapy, utility was further adjusted for the 6 months of administration.[33-35] Patients experiencing recurrence had further decrements in utility (Table 1).

The costs of the Oncotype DX test ($3,416) were based on the Medicare reimbursement rate.[38] Age- and stage-specific cancer care costs were based on published national estimates.[38-40,44] Initial care costs were separated into initial care with and without chemotherapy (including toxicity) on the basis of age- and stage-specific proportions of patients receiving chemotherapy nationally. Costs of treatment of chemotherapy toxicity were assumed to include a short hospitalization and emergency room visits for evaluation of adverse events.[25]

Patients who experienced a distant recurrence were assumed to incur new chemotherapy costs.[2] On the basis of a median overall survival after distant recurrence of 36 months,[45,46] recurrence costs included 1 year of chemotherapy, 1 year of continuing care, and 1 year of terminal care. Patients without recurrence incurred continuing care costs until the last year of life; they then incurred terminal care costs on the basis of those of the noncancer population.[39]

Patient time costs for chemotherapy were based on travel and time for standard regimens.[41,42] Time costs for the treatment of toxicity were based on the average length of a hospital stay (eg, for febrile neutropenia) and/or number of emergency room visits. Patient time was valued using the average 2012 US female hourly wage rate.[43] All costs were updated to 2015 US dollars (the most current year available) using the medical care component of the Consumer Price Index.[47] Future costs and QALYs were discounted at 3%.

Analyses

One hundred million simulations were conducted to reduce Monte Carlo error in the estimation of costs and effects. We calculated the incremental cost-effectiveness ratio for community Oncotype DX test and chemotherapy treatment patterns versus usual care in the pre–Oncotype DX era.

Accounting for Uncertainty

To evaluate the impact of uncertainty, we conducted several one-way sensitivity analyses. First, we examined the impact of test misclassification of distant recurrence by varying results across the upper and lower 95% CIs of the derived test operating characteristics for accuracy. Because there were three possible categories of recurrence risk scores (low, intermediate, and high) conditional on two recurrence possibilities (yes or no), to estimate the least misclassification of low-risk scores given no recurrence, the highest probability of having a low-risk score was combined with the lowest probability for having a high-risk score. For the least misclassification of high-risk given recurrence, the highest probability of having a high-risk score was combined with the lowest probability of having a low-risk score. In each calculation, the total is constrained to equal 1, so that the probability of intermediate risk was 1 minus the sum of the probability of the high-risk and low-risk scores.

Next, we varied the cost of the Oncotype DX test from $2,657 to $4,175 on the basis of the difference (± $759) between the retail price of $4,175 and the Medicare reimbursement rate ($3,416). To assess the impact of perfect patient adherence to test-suggested treatment, 100%, 50%, and 0% chemotherapy use was assumed among those with high-, intermediate-, and low-risk scores, respectively.

Scenario Analyses

We assessed the following two alternative scenarios to the base-case analyses: using the insurer (ie, Medicare) perspective by excluding patient time costs, and including the net impact of Oncotype DX testing on possible reassurance or worry about distant recurrence through further utility weighting. For the latter, we assumed that over the first 2 years after diagnosis, patients with low-risk scores gained 0.05 QALY as a result of a decrease in worry, whereas patients with high-risk scores had a 0.05 reduction in QALYs as a result of increased worry about recurrence.[48]

Finally, we conducted a multiway sensitivity analysis of a scenario with the following idealized conditions: 100% test rates and adherence to test-suggested chemotherapy treatment, best test accuracy, inclusion of the impact of testing on utility, and lowest costs. We did not perform a probabilistic sensitivity analysis because the computational burden exceeded available computing resources.

Model Validation

To evaluate the validity of the model outcomes, the code was verified by confirming that results varied in expected directions using extreme values of parameters. Face validity was evaluated by comparing life-years saved among clinically relevant patient subgroups on the basis of age, stage, recurrence, and chemotherapy use (Appendix Table A1, online only).

RESULTS

Community practice Oncotype DX test and chemotherapy rates between 2005 and 2012 were 24.2% and 30.0%, respectively. Tested patients were younger than nontested patients (mean age, 56.2 years [standard deviation, 8.9 years] *v* 60.7 years [standard deviation, 10.1 years], respectively) and more likely to have stage I disease than stage II disease (data not shown). Tested patients younger than age 50 years had lower chemotherapy rates than untested patients in the same age group (53.0% *v* 63.6%, respectively). Among older patients, there was more chemotherapy use among tested than

Table 1. Model Input Parameters for Estimation of Costs and Effects Among Patients With ER-Positive, HER2-Negative, Lymph Node–Negative, Stage I or IIA Breast Cancer

Parameter	Value, Range, or Description	Description and Source
Life tables for the multiple cohorts	Cohort born in 1936-1975; age 40-79 in 2015	US national data[20]
Age- and stage-specific distribution of ER-positive/HER2-negative breast cancers		US national data[21]
Probability of distant recurrence among ER-positive/HER2-negative patients, conditioned on stage and age		Modeled national data based on US cancer survival data[22,23]
Stage I		
40-49 years	0.2170	
50-59 years	0.2437	
60-69 years	0.2382	
≥ 70 years	0.2358	
Stage II (node negative)		
40-49 years	0.3528	
50-59 years	0.3870	
60-69 years	0.3778	
≥ 70 years	0.3702	
Oncotype DX test results conditional on recurrence/nonrecurrence		Data from the NSABP trial used for validation of clinical predictive utility of Oncotype DX testing[3]
Pr(Category | Recur) (95% CI)		
Low	0.2340 (0.08 to 0.387)	
Intermediate	0.2120 (0.055 to 0.369)	
High	0.5550 (0.430 to 0.679)	
Pr(Category | Not Recur) (95% CI)		
Low	0.5580 (0.518 to 0.599)	
Intermediate	0.2210 (0.155 to 0.287)	
High	0.2200 (0.155 to 0.286)	
Probability of chemotherapy use conditional on age, stage, and testing result		Logistic regression model based on integrated health care plan data[8]
Stage I		
Untested		
40-49 years	0.4926	
50-64 years	0.210	
≥ 65 years	0.0427	
Low		
40-49 years	0.1253	
50-64 years	0.0358	
≥ 65 years	0.0065	
Intermediate		
40-49 years	0.6034	
50-64 years	0.2828	
≥ 65 years	0.0654	
High		
40-49 years	0.8910	
50-64 years	0.6794	
≥ 65 years	0.2732	
Stage II (node negative)		
Untested		
40-49 years	0.8329	
50-64 years	0.5636	
≥ 65 years	0.1864	
Low		
40-49 years	0.4237	
50-64 years	0.1600	
≥ 65 years	0.0327	
Intermediate		
40-49 years	0.8865	
50-64 years	0.6693	
≥ 65 years	0.2642	
High		
40-49 years	0.9767	
50-64 years	0.9158	
≥ 65 years	0.6587	

(continued on following page)

Table 1. Model Input Parameters for Estimation of Costs and Effects Among Patients With ER-Positive, HER2-Negative, Lymph Node–Negative, Stage I or IIA Breast Cancer (continued)

Parameter	Value, Range, or Description	Description and Source
Rates of chemotherapy toxicity by age (range)		Published clinical trial data for common therapy[24-28]
Grade 3 or 4		
< 65 years	0.1115 (0.04-0.1830)	
≥ 65 years	0.1490 (0.08-0.2179)	
Grade 5		
< 65 years	0.0015 (0-0.003)	
≥ 65 years	0.0145 (0.0136-0.0153)	
Breast cancer–specific survival rate by age and stage in the absence of systemic therapy		Modeled national data based on US cancer survival data[22,23]
No recurrence	Infinite (cured)	
Recurrence	25-year breast cancer survival before adjuvant treatment by joint ER/HER2 status, age group, and AJCC stage	
Reduction in hazard of death with hormonal therapy alone or hormonal therapy plus chemotherapy	Survival after treatment is modeled by reducing the hazard ratio of the survival function in the absence of treatment of those who were not cured by initial treatment and adjuvant therapy	Oxford overview of clinical trials[29]
Other cause competing mortality	Age specific	US mortality data[30]
Base age-specific utility for US women (range)		EQ-5D population data[31,32]
20-25 years	0.913 (0.905-0.920)	
30-35 years	0.893 (0.886-0.900)	
40-45 years	0.863 (0.855-0.871)	
50-55 years	0.837 (0.829-0.846)	
60-65 years	0.811 (0.800-0.822)	
70-75 years	0.771 (0.758-0.784)	
80-85 years	0.724 (0.701-0.747)	
Age-specific utilities for cancer states		Studies[33-27] and expert opinion
Chemotherapy	0.9 (6-month duration)	
Experience toxicity	0.7 (6-month duration)	
Reassurance	+0.05 QALY per year	
Worry	−0.05 QALY per year	
Recurrence	0.4 (≤ 3 years)	
Cost* of Oncotype DX (range)	$3,416 ($2,657-$4,175)	Medicare[38]
Cost of initial cancer care phase†		SEER-Medicare data[35,39]
With chemotherapy		
Age < 65 years	$40,987	
Age ≥ 65 years	$38,997	
Without chemotherapy		
Age < 65 years	$28,648	
Age ≥ 65 years	$26,145	
Cost of chemotherapy toxicity treatment†	$17,113	Published studies[25]
Cost of recurrence therapy	$64,320	Published studies[40]
Cost of continuing cancer care phase†		SEER-Medicare data[39,41]
Age < 65 years	$2,539	
Age ≥ 65 years	$2,539	
Cost of terminal care phase†		SEER-Medicare data[39,41]
With breast cancer death		
Age < 65 years	$108,914	
Age ≥ 65 years	$72,610	
Without breast cancer death		
Age < 65 years	$860	
Age ≥ 65 years	$860	
Patient time costs		Published studies[41-43]
Chemotherapy	$588	
Chemotherapy toxicity treatment	$1,215	

Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NSABP, National Surgical Adjuvant Breast and Bowel Project; QALY, quality-adjusted life-year.
*All costs are adjusted to 2015 dollars.
†Patients of all ages diagnosed with ER-positive breast cancer from 2005 to 2012.[39]

untested patients (age 50 to 64 years: 36.5% *v* 30.8%, respectively; age ≥ 65 years: 17.6% *v* 8.2%, respectively; Table 2). These patterns resulted in a greater proportion of tested than untested patients who were destined to have distant recurrences receiving chemotherapy (55.3% *v* 30.4%, respectively).

Incremental Cost Effectiveness

The incremental cost-effectiveness ratio of breast cancer management using Oncotype DX testing as observed in community practice versus usual care without testing was $188,125 per QALY (Table 3). However, varying the values of several factors changed the results substantially, in several cases decreasing the costs to < $75,000 per QALY (Fig 2 and Appendix Table A2, online only). For instance, if Oncotype DX costs were decreased from current Medicare reimbursement rates of $3,416 to $2,657, then the incremental cost-effectiveness ratio of community practice versus usual care decreased to $71,250 per QALY. If Oncotype DX test properties improved, the incremental cost-effectiveness ratio decreased to $28,947 per QALY. If testing had the worst-case accuracy, testing would be dominated (ie, costs more and saves fewer lives than usual care).

Under the assumption that having information about recurrence risk affects utilities via worry or reassurance, the incremental cost-effectiveness ratio for Oncotype DX testing as it occurred in community practice versus usual care was $58,431 per QALY gained (Fig 2 and Appendix Table A2). Adherence to test-concordant treatment lowered the cost-effectiveness ratio to $85,490 per QALY, but the insurers' perspective had less of an effect on the cost-effectiveness ratio ($207,500 per QALY). Finally, in the multiway scenario analyses of ideal circumstances, the likely cost-effectiveness ratio for Oncotype DX testing would be $39,496 per QALY compared with usual care without testing (not shown).

DISCUSSION

This study evaluated the likely cost effectiveness of Oncotype DX testing as integrated into breast cancer care in community practice versus usual care without testing for patients diagnosed with early-stage, ER-positive, HER2-negative breast cancer. The patterns of Oncotype DX use in community practice suggest that there was selection of patients to testing where results may have been most likely to affect treatment decisions. Although Oncotype DX testing has high costs relative to its benefits as deployed in community practice, realistic variations in assumptions about key variables could result in testing having cost-effectiveness ratios in the range of other generally accepted interventions. The variables that resulted in lower cost-effectiveness ratios for community use of Oncotype DX than seen in the base case included lower test costs, higher test accuracy, greater adherence to test-suggested treatment, and consideration of the benefits of testing on quality of life.

GEP testing is primarily recommended to support decisions about adjuvant chemotherapy. Although only 22% to 42% of test-eligible patients undergo Oncotype DX testing in the United States,[4-9] the patterns of care in our study suggest that testing is being used in situations where results are most likely to change management. For instance, although older women were less likely to be tested than younger women, older women who were tested were twice as likely to receive chemotherapy as those who were not tested, especially when they had high recurrence risk scores. In addition, among younger patients in whom chemotherapy is typically recommended, many who were tested and had low-risk results avoided chemotherapy.

The cost-effectiveness ratio in this study is substantially higher than that reported in past analyses of Oncotype DX.[12-14,16] This difference is likely to be the result of several factors. First, past studies assumed ideal conditions and/or large reductions in chemotherapy use with testing.[12-14,16] We found that although rates of chemotherapy decreased in community practice after the introduction of Oncotype DX testing,[8] testing did not change decisions about chemotherapy as dramatically as earlier analyses assumed it would. Second, in contrast to the assumptions in prior analyses, not all patients who were tested followed the test-suggested decision about chemotherapy.[11,16] Moreover, in community practice, fewer women were receiving chemotherapy under usual care before the introduction of testing than assumed in the earlier studies.

This study was unique in considering the impact of test properties on cost-effectiveness ratios, whereas past analyses generally

Table 2. Chemotherapy Rates by Age and Oncotype DX Test Use and Recurrence Outcomes in Community Practice With Testing and Usual Care in the Pre–Oncotype DX Era Among Patients with Stage I or IIa, Node-Negative, ER-Positive/HER2-Negative Breast Cancer

	Rate of Chemotherapy Use (%)					
	All Patients			Recurrence*	No Recurrence	Overall
Status	Age 40-49 Years	Age 50-64 Years	Age ≥ 65 Years	Age 40-79 Years	Age 40-79 Years	Age 40-79 Years
Community practice with testing (2005-2012)						
All patients	60.0	32.5	9.1	36.5	27.5	30.0
Untested (75.8%)	63.6	30.8	8.2	30.4	26.2	27.4
Tested (24.2%)	53.0	36.5	17.6	55.3	31.5	38.1
Risk category among tested						
Low	20.8	7.3	1.6	11.7	9.9	10.2
Intermediate	68.5	40.7	14.1	47.2	43.2	44.3
High	91.9	76.4	43.4	76.7	74.2	75.3
Usual care without test (2000-2004)						
Untested (100%)	65.5	37.3	9.9	36.9	33.3	33.6
Tested	NA	NA	NA	NA	NA	NA

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NA, not applicable.
*Recurrence is not know to clinicians and patients when making chemotherapy use decisions; the use of chemotherapy noted on the table is calculated among those who ultimately recur or not and is based on modeled outcomes[22,23]

Table 3. Societal Perspective Incremental Cost-Effectiveness Ratio of Oncotype Testing in Community Practice Versus Usual Care Without Testing Among Patients With Stage I or II, Node-Negative, ER-Positive, HER2-Negative Breast Cancer

Test Use	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	Incremental Cost per QALY ($)
Usual care without test	90,879		10.4710		
Community practice test use	91,180	301	10.4726	0.0016	188,125

NOTE. Year 2015 US dollars; all costs and effects discounted at 3%.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; QALY, quality-adjusted life-year.

assumed perfect prediction of recurrence.[12,14,16] In fact, the original validation study found that 70% of patients with high-risk scores did not develop distant recurrence and 7% of patients at low risk had distant recurrences at 10 years.[3] When we examined idealized conditions, including perfect test accuracy, the cost-effectiveness ratio decreased to $39,496 per QALY, which is more similar to earlier estimates, given inflation.[13,14]

We examined Oncotype DX in this study, but there are several other GEP tests being promoted for clinical use.[49-53] Consequently, it is possible that market forces will decrease future GEP test costs. This analysis demonstrated that if Oncotype DX test costs were lower than present Medicare reimbursement rates, it would have cost-effectiveness ratios similar to many currently covered services.[54,55]

A novel contribution of this analysis is the consideration of the impact on the cost-effectiveness ratio of the potential ability of GEP testing to provide reassurance if results indicate a low risk of recurrence (or to increase worry with high-risk results). Given that the majority of patients for whom testing is currently recommended will have low recurrence risk scores, the increase in QALYs from reassurance outweighed any decrease as a result of increasing worry among those with high-risk scores. Consideration of these effects lowered the cost-effectiveness ratio to $58,431. Because our result was based on expert opinion, further research is warranted to determine patient utility and willingness to pay related to this aspect of GEP testing. Furthermore, because selection of test result–concordant therapy affects cost-effectiveness ratios, future studies should explore reasons for discordance between treatment prescribed by GEP results and actual treatments received.

There are several caveats that should be considered in evaluating our results. First, the cost-effectiveness results for community practice used data from a large integrated health plan for GEP testing and chemotherapy rates because there is no national source of community data with registry information, GEP results, and complete chemotherapy data. The data used in this analysis may not generalize to other community settings if financial barriers and other practice factors cause different patterns of patient selection

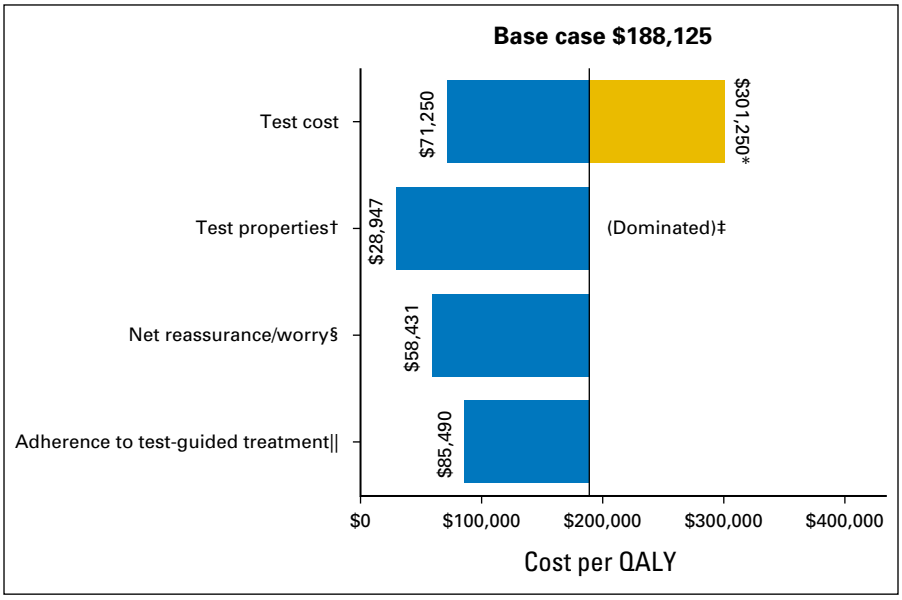

Fig 2. Impact of varying single parameters on the societal cost-effectiveness ratios for Oncotype DX testing in community practice versus usual care without testing among patients with stage I or II, node-negative, estrogen receptor–positive, human epidermal growth factor receptor 2–negative breast cancer. This diagram illustrates the changes in the incremental cost-effectiveness ratio (ICER) for the costs per quality-adjusted life-year (QALY) under various parameter values and alternative assumptions. The solid vertical line represents the base-case ICER result comparing community practice with Oncotype DX testing versus usual care without Oncotype DX. The horizontal bars indicate the change from the base ICER when the one individual parameter is varied. If the bar goes to the right of the base case, it indicates that the alternative value or assumption costs more per QALY than the base case, where bars that go to the left indicate that the alternative value or assumption costs less per QALY than the base case. (*) Test costs were varied from the base case of $3,416 to $2,657 and $4,175. The large difference in cost per QALY when test costs were varied is a result of these effects being magnified by the small incremental QALYs between usual care and community care. (†) The accuracy of the test represents the probability of a test score, conditional on actual distant recurrence. The best test accuracy reflects a greater proportion of women who actually experience recurrence having high-risk scores and a smaller proportion having low-risk scores, and among those who do not experience recurrence, fewer have high-risk scores and more have low-risk scores than in the base case on the basis of observed performance in the original validation study. (‡) The worst testing accuracy was dominated. That is, it resulted in community practice being more costly and producing fewer QALYs than usual care without testing. (§) Net reassurance/worry is based on gaining 0.5 QALY or losing 0.5 QALY over the first 2 years after diagnosis with low- and high-risk recurrence scores, respectively. (||) One hundred percent adherence to test-guided treatment assumes 100% chemotherapy use among patients with high-risk score on gene expression profile testing, 50% chemotherapy use for intermediate risk, and 0% chemotherapy use for low risk.

to testing and/or differentially affect events downstream from the decision to use GEP testing. Therefore, costs and effects in other community settings could be better or worse than estimated in this analysis. However, data from the patients included in the integrated health plan have been shown to be representative of the US population in terms of sociodemographic and cancer characteristics,[8,56,57] and the patterns of Onco*type* DX use and treatment are similar to those reported in other care settings.[58]

Second, GEP testing does not have a direct effect on survival. GEP testing can only affect QALYs by guiding a greater use of chemotherapy to the small proportion of women at highest risk of recurrence who would not otherwise be treated without testing. Hence, the difference in QALYs between tested and untested patients in this analysis is small. In these situations, factors that lead to even small differences in QALYs between community practice and usual care can magnify differences in the cost-effectiveness ratios. Finally, it will be important to reassess the cost-effectiveness ratios for GEP testing as results of the predictive validity for intermediate-risk scores[59,60] and node-positive disease become available.[59-61]

Overall, this economic analysis found that the likely cost-effectiveness ratio for Onco*type* DX testing in community practice versus usual care without testing was higher than the ratios for most commonly accepted diagnostic and preventive interventions. However, plausible changes in several factors could change the results and lead to Onco*type* DX testing having a cost-effectiveness ratio similar to other commonly accepted practices. The substantial differences in conclusions about cost-effectiveness ratios on the basis of community practice versus more idealized practice underscore the importance of considering real-world implementation when assessing the costs and survival associated with new diagnostic (or treatment) technology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Young Chandler, Clyde B. Schechter, Charles E. Phelps, Tracy A. Lieu, Scott Ramsey, Jeanne S. Mandelblatt
Administrative support: Aimee Near, Jeanne S. Mandelblatt
Collection and assembly of data: G. Thomas Ray, Tracy A. Lieu, Jeanne S. Mandelblatt
Data analysis and interpretation: Young Chandler, Clyde B. Schechter, Jinani Jayasekera, Aimee Near, Suzanne C. O'Neill, Claudine Isaacs, Charles E. Phelps, Tracy A. Lieu, Scott Ramsey, Jeanne S. Mandelblatt
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. ASCO Institute for Quality: Breast cancer treatment plan and summary resources. http://www.instituteforquality.org/breast-cancer-treatment-plan-and-summary-resources
2. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Breast Cancer. Version 2.2017. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
3. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351:2817-2826, 2004
4. Afghahi A, Mathur M, Thompson CA, et al: Use of gene expression profiling and chemotherapy in early-stage breast cancer: A study of linked electronic medical records, cancer registry data, and genomic data across two health care systems. J Oncol Pract 12:e697-e709, 2016
5. Epstein AJ, Wong YN, Mitra N, et al: Adjuvant chemotherapy use and health care costs after introduction of genomic testing in breast cancer. J Clin Oncol 33:4259-4267, 2015
6. O'Neill SC, Isaacs C, Chao C, et al: Adoption of gene expression profiling for breast cancer in US oncology practice for women younger than 65 years. J Natl Compr Canc Netw 13:1216-1224, 2015
7. Orucevic A, Heidel RE, Bell JL: Utilization and impact of 21-gene recurrence score assay for breast cancer in clinical practice across the United States: Lessons learned from the 2010 to 2012 National Cancer Data Base analysis. Breast Cancer Res Treat 157:427-435, 2016
8. Ray GT, Mandelblatt J, Habel LA, et al: Breast cancer multigene testing trends and impact on chemotherapy use. Am J Manag Care 22:e153-e160, 2016
9. Su KW, Hall J, Soulos PR, et al: Association of 21-gene recurrence score assay and adjuvant chemotherapy use in the Medicare population, 2008-2011. J Geriatr Oncol 7:15-23, 2016
10. Carlson JJ, Roth JA: The impact of the Onco*type* Dx breast cancer assay in clinical practice: A systematic review and meta-analysis. Breast Cancer Res Treat 141:13-22, 2013
11. Hornberger J, Cosler LE, Lyman GH: Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer. Am J Manag Care 11:313-324, 2005
12. Blohmer JU, Rezai M, Kümmel S, et al: Using the 21-gene assay to guide adjuvant chemotherapy decision-making in early-stage breast cancer: A cost-effectiveness evaluation in the German setting. J Med Econ 16:30-40, 2013
13. Hall PS, McCabe C, Stein RC, et al: Economic evaluation of genomic test-directed chemotherapy for early-stage lymph node-positive breast cancer. J Natl Cancer Inst 104:56-66, 2012
14. Klang SH, Hammerman A, Liebermann N, et al: Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. Value Health 13:381-387, 2010
15. Kondo M, Hoshi SL, Ishiguro H, et al: Economic evaluation of 21-gene reverse transcriptase-polymerase chain reaction assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer in Japan. Breast Cancer Res Treat 112:175-187, 2008
16. Lyman GH, Cosler LE, Kuderer NM, et al: 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. Cancer 109:1011-1018, 2007
17. Tsoi DT, Inoue M, Kelly CM, et al: Cost-effectiveness analysis of recurrence score-guided treatment using a 21-gene assay in early breast cancer. Oncologist 15:457-465, 2010
18. National Cancer Institute: SEER Program: Cancer Stat Facts: Female Breast Cancer. https://seer.cancer.gov/statfacts/html/breast.html
19. Esserman LJ, Moore DH, Tsing PJ, et al: Biologic markers determine both the risk and the timing of recurrence in breast cancer. Breast Cancer Res Treat 129:607-616, 2011
20. Carter SB, Gartner SS, Haines MR, et al: Historical Statistics of the United States: Millennial Edition (Online Version). Volume One: Population. New York, NY, Cambridge University Press, 2006
21. National Cancer Institute: SEER Program: SEER*stat databases: Incidence - SEER 9 regs research data, November 2015 submission (1973-2013). https://seer.cancer.gov/data/seerstat/nov2015/
22. Munoz D, Plevritis SK: Estimating breast cancer progression features and survival by molecular subtype in the absence of screening and treatment. Med Decis Making (in press)
23. Munoz D, Near AM, van Ravesteyn NT, et al: Effects of screening and systemic adjuvant therapy on ER-specific US breast cancer mortality. J Natl Cancer Inst 106:dju289, 2014
24. De Maio E, Gravina A, Pacilio C, et al: Compliance and toxicity of adjuvant CMF in elderly breast cancer patients: A single-center experience. BMC Cancer 5:30, 2005
25. Hassett MJ, O'Malley AJ, Pakes JR, et al: Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer. J Natl Cancer Inst 98:1108-1117, 2006
26. Jones S, Holmes FA, O'Shaughnessy J, et al: Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin

and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. J Clin Oncol 27: 1177-1183, 2009

27. Muss HB, Berry DA, Cirrincione C, et al: Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: The Cancer and Leukemia Group B experience. J Clin Oncol 25:3699-3704, 2007

28. Muss HB, Berry DA, Cirrincione CT, et al: Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 360:2055-2065, 2009

29. Peto R, Davies C, Godwin J, et al: Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 379:432-444, 2012

30. Gangnon RE, Stout NK, Alagoz O, et al: Contribution of breast cancer to overall mortality for U.S. women. Med Decis Making (in press)

31. Agency for Healthcare Research and Quality: Medical expenditure panel survey. https://meps.ahrq.gov/mepsweb/

32. Hanmer J, Lawrence WF, Anderson JP, et al: Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making 26: 391-400, 2006

33. de Haes JC, de Koning HJ, van Oortmarssen GJ, et al: The impact of a breast cancer screening programme on quality-adjusted life-years. Int J Cancer 49:538-544, 1991

34. Earle CC, Chapman RH, Baker CS, et al: Systematic overview of cost-utility assessments in oncology. J Clin Oncol 18:3302-3317, 2000

35. Stout NK, Lee SJ, Schechter CB, et al: Benefits, harms, and costs for breast cancer screening after US implementation of digital mammography. J Natl Cancer Inst 106:dju092, 2014

36. Mandelblatt JS, Stout NK, Schechter CB, et al: Collaborative modeling of the benefits and harms associated with different U.S. breast cancer screening strategies. Ann Intern Med 164:215-225, 2016

37. Stout NK, Rosenberg MA, Trentham-Dietz A, et al: Retrospective cost-effectiveness analysis of screening mammography. J Natl Cancer Inst 98: 774-782, 2006

38. Centers for Medicaid and Medicare Services: Clinical laboratory fee schedule. https://www.cms.gov/medicare/medicare-fee-for-service-payment/clinicallabfeesched/

39. Mariotto AB, Yabroff KR, Shao Y, et al: Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst 103:117-128, 2011

40. Stokes ME, Thompson D, Montoya EL, et al: Ten-year survival and cost following breast cancer recurrence: Estimates from SEER-Medicare data. Value Health 11:213-220, 2008

41. Yabroff KR, Davis WW, Lamont EB, et al: Patient time costs associated with cancer care. J Natl Cancer Inst 99:14-23, 2007

42. Secker-Walker RH, Vacek PM, Hooper GJ, et al: Screening for breast cancer: Time, travel, and out-of-pocket expenses. J Natl Cancer Inst 91: 702-708, 1999

43. US Bureau of Labor Statistics: Median weekly earnings of full-time wage and salary workers by detailed occupation and sex. https://www.bls.gov/cps/cpsaat39.htm

44. Yabroff KR, Lamont EB, Mariotto A, et al: Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst 100:630-641, 2008

45. Finn RS, Crown JP, Lang I, et al: The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study. Lancet Oncol 16: 25-35, 2015

46. Zeichner SB, Herna S, Mani A, et al: Survival of patients with de-novo metastatic breast cancer: Analysis of data from a large breast cancer-specific private practice, a university-based cancer center and review of the literature. Breast Cancer Res Treat 153: 617-624, 2015

47. US Bureau of Labor: Consumer Price Index. https://www.bls.gov/cpi/home.htm

48. Raldow AC, Sher D, Chen AB, et al: Cost effectiveness of the Onco*type* DX DCIS Score for guiding treatment of patients with ductal carcinoma in situ. J Clin Oncol 34:3963-3968, 2016

49. Cardoso F, van't Veer LJ, Bogaerts J, et al: 70-gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 375:717-729, 2016

50. Esteva FJ, Sahin AA, Cristofanilli M, et al: Prognostic role of a multigene reverse transcriptase-PCR assay in patients with node-negative breast cancer not receiving adjuvant systemic therapy. Clin Cancer Res 11:3315-3319, 2005

51. Ignatiadis M, Azim HA Jr, Desmedt C, et al: The genomic grade assay compared with Ki67 to determine risk of distant breast cancer recurrence. JAMA Oncol 2:217-224, 2016

52. Martin M, Brase JC, Calvo L, et al: Clinical validation of the EndoPredict test in node-positive, chemotherapy-treated ER+/HER2- breast cancer patients: Results from the GEICAM 9906 trial. Breast Cancer Res 16:R38, 2014

53. Sgroi DC, Sestak I, Cuzick J, et al: Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: A prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. Lancet Oncol 14:1067-1076, 2013

54. Institute for Clinical and Economic Review: ICER value assessment framework: 1.0 to 2.0. http://icer-review.org/wp-content/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINAL.pdf

55. Neumann PJ, Sanders GD: Cost-Effectiveness Analysis 2.0. N Engl J Med 376:203-205, 2017

56. Kurian AW, Munoz DF, Rust P, et al: Online tool to guide decisions for BRCA1/2 mutation carriers. J Clin Oncol 30:497-506, 2012

57. Oehrli MD, Quesenberry CP, Leyden W: 2006 annual report on trends, incidence, and outcomes. Kaiser Permanente, Northern California Cancer Registry. https://www.scienceopen.com/document?vid=993b2113-bcec-4a0e-b017-617fa63dcbd7

58. Potosky AL, O'Neill SC, Isaacs C, et al: Population-based study of the effect of gene expression profiling on adjuvant chemotherapy use in breast cancer patients under the age of 65 years. Cancer 121:4062-4070, 2015

59. Jasem J, Fisher CM, Amini A, et al: The 21-gene recurrence score assay for node-positive, early-stage breast cancer and impact of RxPONDER trial on chemotherapy decision-making: Have clinicians already decided? J Natl Compr Canc Netw 15:494-503, 2017

60. Paik S: Development and clinical utility of a 21-gene recurrence score prognostic assay in patients with early breast cancer treated with tamoxifen. Oncologist 12:631-635, 2007

61. Ramsey SD, Barlow WE, Gonzalez-Angulo AM, et al: Integrating comparative effectiveness design elements and endpoints into a phase III, randomized clinical trial (SWOG S1007) evaluating Onco*type*DX-guided management for women with breast cancer involving lymph nodes. Contemp Clin Trials 34:1-9, 2013

Affiliations

Young Chandler, **Jinani Jayasekera**, **Aimee Near**, **Suzanne C. O'Neill**, **Claudine Isaacs**, and **Jeanne S. Mandelblatt**, Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, DC; **Clyde B. Schechter**, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx; **Charles E. Phelps**, University of Rochester, Rochester, NY; **G. Thomas Ray** and **Tracy A. Lieu**, Kaiser Permanente Northern California, Oakland, CA; and **Scott Ramsey**, Fred Hutchinson Cancer Research Center, Seattle, WA.

Support

Supported by National Cancer Institute Grant No. UO1 CA183081 (J.M., T.A.L., and S.R.) and American Cancer Society Mentored Research Scholar Grant No. 14-027-01-CPHPS (Y.C.). Also supported, in part, by Grant No. U01 CA152958 from the National Cancer Institute as part of the Cancer Intervention and Surveillance Modeling Network, Grant No. R35CA197289 (J.M.) from the National Cancer Institute, Grant No. UC2 CA148471 (Katrina Goddard, Lawrence Kushi, and Evelyn Whitlock) from the National Cancer Institute, Grant No. R01 CA105274 (Lawrence Kushi) from the National Cancer Institute, Lombardi Comprehensive Cancer Center American Cancer Society Young Investigator Award No. ACS IRG 92-152-20 (J.J.), and a Cancer Prevention Research Fellowship sponsored by the American Society of Preventive Oncology and the Breast Cancer Research Foundation (ASPO-17-001; J.J.).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cost Effectiveness of Gene Expression Profile Testing in Community Practice

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Young Chandler
No relationship to disclose

Clyde B. Schechter
Consulting or Advisory Role: COHRDATA

Jinani Jayasekera
No relationship to disclose

Aimee Near
No relationship to disclose

Suzanne C. O'Neill
No relationship to disclose

Claudine Isaacs
Consulting or Advisory Role: Pfizer, Genentech, Novartis, AstraZeneca, Medivation, NanoString Technologies
Speakers' Bureau: Genentech, Celgene, Pfizer, AstraZeneca
Research Funding: Novartis (Inst), Pfizer (Inst), Genentech (Inst), Tesaro (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate
Travel, Accommodations, Expenses: Caris Life Sciences

Charles E. Phelps
No relationship to disclose

G. Thomas Ray
Employment: The Permanente Medical Group
Research Funding: Pfizer (Inst)

Tracy A. Lieu
No relationship to disclose

Scott Ramsey
Consulting or Advisory Role: Bayer, Genentech, Bristol-Myers Squibb
Research Funding: Genentech
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Bayer

Jeanne S. Mandelblatt
No relationship to disclose

Acknowledgment

We thank Yan Li, MD, Laurie Habel, PhD, and Lawrence Kushi, ScD, for prior work integrating Onco*type* DX results with Kaiser Permanente Northern California data and for thoughtful suggestions on earlier versions of this article.

Appendix

Table A1. Model Outcomes for Life-Years Among Patients With Stage I or II, Node-Negative, ER-Positive, HER2-Negative Breast Cancer by Chemotherapy, Age, Stage, and Recurrence

	Stage I (No. of LY)		Stage II (No. of LY)	
Age Group (years)	Chemotherapy	No Chemotherapy	Chemotherapy	No Chemotherapy
All patients				
40-49	21.92	22.04	20.77	20.70
50-64	20.01	19.99	18.96	18.83
65-79	15.56	15.62	14.72	14.66
Experienced recurrence				
40-49	16.28	14.1	15.47	13.21
50-64	16.17	14.45	15.22	13.36
65-79	13.05	12.1	12.3	11.18
No recurrence				
40-49	23.81	23.86	23.82	23.87
50-64	21.60	21.62	21.64	21.67
65-79	16.48	16.71	16.40	16.65

NOTE. This table shows that among those who ultimately experience recurrence (middle rows), chemotherapy increases LYs and that younger patients destined to recur have larger gains in LYs than older patients; those with stage II disease have greater gains than those with stage I disease. Among patients who never experience recurrence (bottom rows), chemotherapy has no effect on LYs. Because most patients with these favorable-prognosis tumors do not experience recurrence and rates of chemotherapy use are low, the overall impact of chemotherapy on LYs (top rows) is small.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LY, life-year.

Table A2. One-Way Sensitivity Analysis: Impact of Varying Single Parameters on the Societal Cost Effectiveness of Oncotype DX Testing Use in Community Care Versus Usual Care Without Testing

Parameter	Cost ($)*	Incremental Cost ($)	QALYs*†	Incremental QALYs	Incremental Cost per QALY ($)
Test cost					
Usual care	90,879		10.471		
Lowest test cost	90,993	114	10.4726	0.0016	71,250
High test cost	91,361	482	10.4726	0.0016	301,250
Test accuracy‡					
Usual care	90,879		10.471		
Best	91,154	275	10.4805	0.0095	28,947
Worst	91,209	330	10.4669	−0.0041	Dominated
Impact on utility					
Usual care	90,879		10.471		
Net reassurance/worry§	91,177	298	10.4761	0.0051	58,431
Adherence					
Usual care	90,879		10.471		
Perfect adherence	91,315	436	10.4761	0.0051	85,490
Insurer perspective					
Usual care	90,631		10.471		
Community care	90,963	332	10.4726	0.0016	207,500

Abbreviation: QALY, quality-adjusted life-year.

*All costs and QALYs discounted at 3%.

†Oncotype Dx testing only increases life-years by increasing chemotherapy use (*v* rates without testing) among those destined to recur (approximately 9% of the overall early-stage estrogen receptor–positive, human epidermal growth factor receptor 2–negative, stage I and II patient population). Hence, there are only minimal overall differences in QALYS among tested and untested patients.

‡The best-case test properties assumed a combination of the greatest probability of a high-risk score and the lowest probability of a low-risk score given recurrence and a combination of the lowest probability of a high-risk score and the highest probability of a low-risk score given no recurrence. The worst-case test properties assumed the reverse in each recurrence group. Because the overall probabilities of having one of the three risk category scores sum to 1, the probability of an intermediate-risk score is as follows: 1 − [sum of the probability of low + high risk]. The Oncotype DX test has good clinical utility but not 100% predictive value or sensitivity. The base case uses the data on test score result category (high, intermediate, and low risk of recurrence) given distant recurrence status from the original study of Oncotype DX.

§Net impact of Oncotype DX testing on utilities via reassurance or worry about distant recurrence. The patients with high-risk score are assumed to have a 0.05 annual reduction in QALY over the first 2 years after diagnosis. The patients with low-risk score are assumed to have a 0.05 annual increase in QALY over the first 2 years after diagnosis.