

Cost-Effectiveness of 21-Gene Assay in Node-Positive, Early-Stage Breast Cancer

Burton F. Vanderlaan, MD; Michael S. Broder, MD; Eunice Y. Chang, PhD;
Ruth Oratz, MD, FACP; and Tanya G. K. Bentley, PhD

Large clinical trials have demonstrated significant benefits of combining chemotherapy with hormonal therapy in the adjuvant treatment of women with node-negative, estrogen receptor-positive (N-/ER+) breast cancer.^{1,2} Hormonal treatment with tamoxifen alone after surgery in this population has been shown to reduce the 10-year likelihood of distant recurrence to 15%.¹ Depending on disease and tumor characteristics, adding chemotherapy can further reduce recurrence risk in some N-/ER+ patients, although others derive no added benefit from adjuvant chemotherapy.^{3,4}

The 21-gene Oncotype DX Recurrence Score reverse transcriptase polymerase chain reaction assay can reliably predict individual recurrence risks among N-/ER+ patients based on gene expression in the tumor tissue.^{5,7} The assay has been incorporated into National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) treatment guidelines for N-/ER+ patients with HER2-negative tumors^{8,9} and has allowed oncologists to move from population-based to individualized estimates of recurrence risk, reducing unnecessary chemotherapy treatment among patients with low predicted recurrence risk.¹⁰⁻¹⁴

In node-positive, estrogen receptor-positive (N+(1-3)/ER+) breast cancer, however, NCCN and ASCO guidelines recommend treatment with both hormonal therapy and chemotherapy for most HER2-negative cancers, although recent research suggests that up to 40% of these patients may remain disease-free without chemotherapy.^{8,9,15} In a recent analysis of the TransATAC study, results of the 21-gene assay were significantly associated with time to distant recurrence and provided significant prognostic value beyond that provided by Adjuvant! Online in both N- and N+(1-3)/ER+ cancers.⁷ In addition, an analysis of the SWOG-8814 clinical trial confirmed the lack of benefit of chemotherapy in women with N+(1-3)/ER+ disease who had low recurrence scores (<18).¹⁵

Better predictions of recurrence risk could help oncologists individualize treatment recommendations. Eliminating chemotherapy for patients unlikely to benefit from it might both decrease costs and improve quality of life.^{11,16-18} We built a decision-analytic model to predict cost-effectiveness and cost savings of using the 21-gene assay Oncotype DX in women with early-stage N+(1-3)(N1a-N1c)/ER+ HER2-negative breast cancer; the cost-effectiveness and cost savings were compared with the

Objective: To assess impact on health outcomes and healthcare expenditures of adopting a 21-gene assay for women with early-stage, minimally node-positive, estrogen receptor-positive (N+(1-3)/ER+) HER2-negative breast cancer.

Study Design: We adapted a deterministic decision-analytic model to estimate costs and quality-of-life outcomes associated with chemotherapy, adverse events, supportive care, recurrence, and second primary cancers for usual care compared with care determined by the 21-gene assay recurrence score, where 71% and 54% of women, respectively, were treated with adjuvant chemotherapy. Model input data were based on national statistics, published literature, physician surveys, and Medicare Part B prices.

Methods: Annual numbers of events were multiplied by quality-adjusted life-years (QALYs) lost and costs to estimate net health and economic impacts of each strategy. Analyses were from a managed care payer perspective for the US population.

Results: Patients receiving the assay were predicted to gain 0.127 QALY and save \$4359 annually from avoiding chemotherapy, adverse events, supportive care, and secondary primary tumors. For a 2-million member plan, net gains were 4.44 QALYs/year and savings were \$13,476/year. Cost savings were greater for the Medicare population. Although overall results were sensitive only to reduced impact of testing and chemotherapy costs, they were still highly cost-effective (incremental cost-effectiveness ratio <\$20,000/QALY).

Conclusions: Use of a 21-gene assay in patients with early-stage N+(1-3)/ER+ HER2-negative breast cancer may improve health outcomes and add no incremental cost, thereby providing valuable insight for health plans, the Centers for Medicare & Medicaid Services, and clinicians regarding coverage policies and treatment decisions.

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Take-Away Points

By providing better predictions of recurrence risk, a 21-gene assay in patients with early-stage N+(1-3)/ER+ HER2-negative breast cancer has the potential to significantly improve US healthcare quality at no additional payer cost.

- Our model predicted that the substantial savings in chemotherapy-related costs would outweigh the cost of the test itself and that patients would experience substantial quality-of-life gains associated with reductions in chemotherapy.

- These results provide insight for health plans, the Centers for Medicare & Medicaid Services, and clinicians when establishing coverage policies and making treatment decisions.

representative of the US population, estimating results for all women with N+(1-3)/ER+ HER2-negative breast cancer. We also evaluated the model for a subset of those 65 years and older. We did not address assay use among patients with N- or HER2+ tumors. Analyses were from a payer (managed care) perspective, and annual risks were based on average risks over a 30-year time horizon.

cost of treating this early-stage breast cancer according to current US guidelines.

Models were developed and analyzed using Microsoft Office Excel 2003 (Redmond, WA).

METHODS

Overview

We adapted a deterministic decision-analytic model (Figure) to estimate the cost-effectiveness of adopting the 21-gene assay in treatment decisions for women with N+(1-3)/ER+ HER2-negative early-stage breast cancer, comparing outcomes for 2 scenarios: usual care, in which chemotherapy treatment decisions reflected historical standards based on US NCCN guidelines; and genomic assay testing, in which decisions were modified based on assay results. The model followed women from being disease free to living with nonprogressed and progressed disease, and then to death either from disease or other causes. Model inputs were obtained from published literature, national statistics, randomized clinical trials, Medicare part B prices, and surveys of breast cancer patients and medical oncologists.

Patients in the model faced risks of being diagnosed with N+(1-3)/ER+ HER2-negative breast cancer with varying recurrence risks; being tested with the 21-gene assay; receiving chemotherapy; experiencing adverse events, second primary cancers, or distal recurrence; and dying within a 30-year time horizon (Table 1). Outcomes of interest were incremental quality-adjusted life-years (QALYs, per patient and total plan), costs (per patient, per member per month, and total plan), and incremental cost-effectiveness associated with the use of the assay in adjuvant chemotherapy treatment decisions. Patients in both usual care and testing strategies either received chemotherapy followed by hormonal therapy or hormonal therapy alone. The single difference between usual care and assay testing strategies was that fewer patients in the testing group received chemotherapy, which in turn affected costs and quality-of-life decrements associated with chemotherapy and related adverse events, supportive care, and second primary cancers.

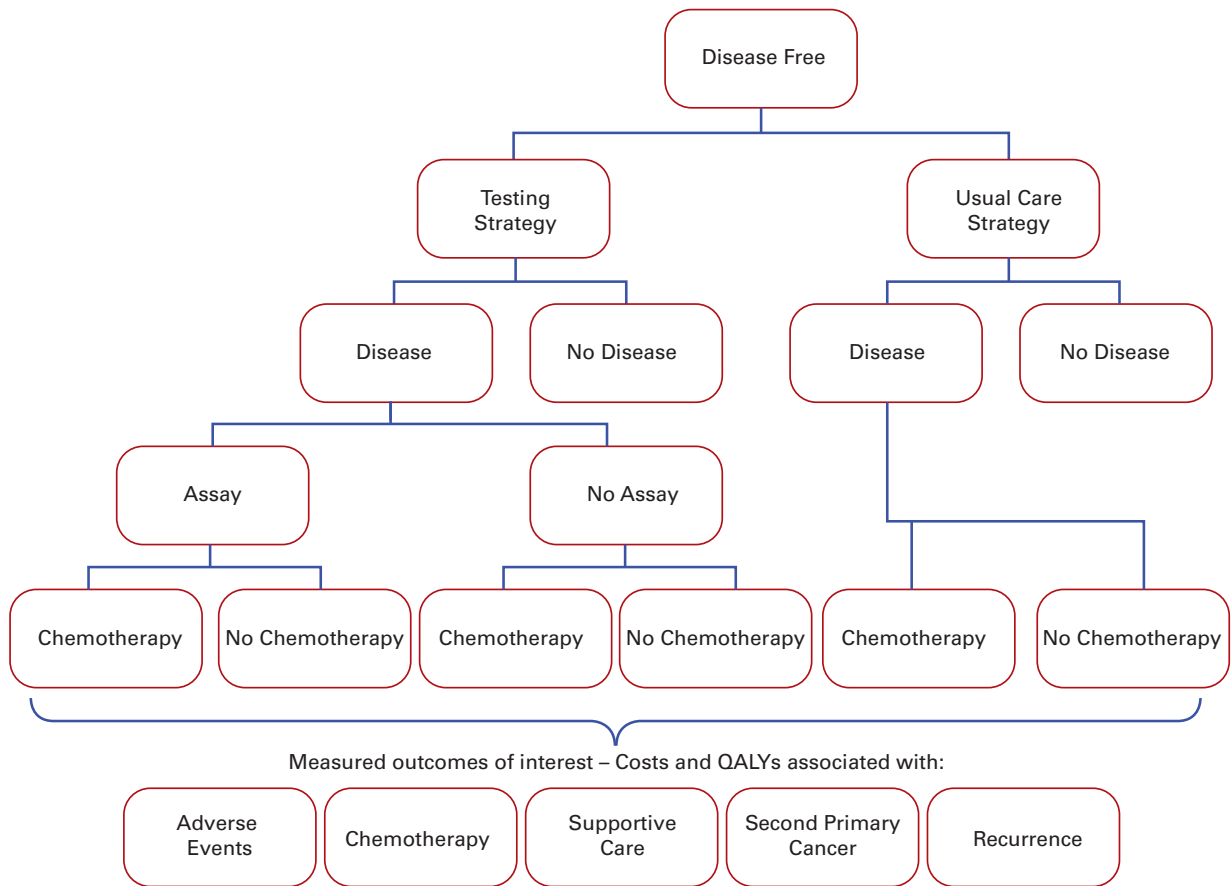
We evaluated the model for a hypothetical cohort of 2 million total health plan members with an age distribution

Data

Table 1 shows parameter estimates used in the deterministic decision-analytic model. We used 2004-2005 SEER*STAT data to estimate an age-adjusted incidence of early-stage N+(1-3)/ER+ breast cancer of 9.74 diagnoses per 100,000 population and a 90% prevalence of HER2-negative tumors, using an age distribution representative of the US population and a mean age of diagnosis of 62 years.¹⁹ We considered women to be N+ if they had 1-3 positive nodes based on evidence that most N+ patients receiving the assay had ≤ 3 positive nodes.²¹ Diagnosed patients in usual care were assumed to be treated according to national guidelines that recommended adjuvant chemotherapy treatment for all N+(1-3)/ER+ patients.⁸ Because some patients may refuse chemotherapy and oncologists may not recommend chemotherapy in all cases (eg, among N1a patients with only 1 positive node), we assumed that 71% of women in usual care would receive chemotherapy treatment.²⁰

In the testing strategy, we assumed that 20% of diagnosed patients would be tested with the assay. Among these patients, we estimated a 24% relative reduction in chemotherapy use associated with assay results based on data from a survey of oncologists who used the assay in this patient population.²¹ Compared with the 71% uptake in usual care, 54% [(1.0 - 0.24 x 71%)] of tested women would receive chemotherapy treatment. A post hoc analysis of the same survey showed a 31% relative reduction in chemotherapy for patients 65 years and older; we thus assumed a 49% chemotherapy rate [(1.0 - 0.31) x 71%] among a subset of tested women in this age group.²⁶ We assumed that the decrease in chemotherapy associated with assay testing occurred only in patients with low recurrent score,^{7,15} so disease recurrence rates did not differ between strategies. Age-specific all-cause mortality was estimated based on national statistics, and for age- and disease-specific mortality we used SEER estimates of overall age-specific breast cancer mortality.^{19,39} These estimates were used to calculate total QALYs lost with each strategy.

Figure. Schematic of Decision-Analytic Cost-Effectiveness Model of a 21-Gene Assay for Minimally Node-Positive Breast Cancer Recurrence Risk^a



QALY indicates quality-adjusted life-year.

^aModel was evaluated for a hypothetical cohort of 2 million total health plan members with an age distribution representative of the US population, and analyses were from a payer (managed care) perspective.

We categorized chemotherapy-related adverse events into minor events, major events, fatal events, and second primary cancers. Minor adverse events were defined as grade ≤ 2 (mild or moderate), where applicable, of the following: chemotherapy-induced nausea and vomiting; neutropenia; thrombocytopenia; diarrhea; alopecia; cardiovascular-functional (defined as any cardiovascular event that was asymptomatic, transient, or responded to treatment); phlebitis; infection; hemorrhagic cystitis; fever; and weight gain or loss. When these adverse events were grade ≥ 3 (severe, life threatening, or fatal), they were considered major, as were neurosensory or neuromotor toxicity, arthralgia, myalgia, granulocytopenia, hypersensitivity reaction, thromboembolic event, ovarian failure, cognitive dysfunction, congestive heart failure, and febrile neutropenia. Any such minor or major events that caused death were considered separately as fatal events.

The incidence of minor adverse events was based on published reports of key trials of anthracycline therapy and an-

tiemetic regimens.^{7,15,28-30,32,35-37} We estimated an 85% minor adverse event rate to account for the higher rates of chemotherapy-induced nausea and vomiting seen in patients receiving some newer regimens and the almost-universal alopecia occurrence seen in patients receiving other regimens.^{35,40} We estimated the probability of major adverse events based on published literature indicating that risk of these events among N+ breast cancer patients ranges between 20% and 35%,^{33,34} and we assumed an average incidence of 30%.

We estimated a 2.7% probability of second primary cancer based on the assumption of a 20-year survival time among diseased patients without recurrence or second primary cancer and a 13.6/10,000 person-years absolute excess risk of second primary nonbreast cancer after treatment ($20 \times 13.6/10,000 = 2.72\%$).^{34,38} Use patterns of chemotherapy-related supportive care (including treatment with granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, erythropoietin, and antiemetics)

Table 1. Population Characteristics and Event Probabilities in a Decision-Analytic Model of a 21-Gene Assay for Determining Adjuvant Chemotherapy Decisions for Early-Stage N+(1-3)/ER+ Breast Cancer^a

Model Parameter	Estimate	Value for Sensitivity Analyses	Reference
Mean age at diagnosis (US population)	62 y	72 y	—
Population size	2,000,000	—	—
Time horizon	30 y	—	—
Annual discount rate	3%	—	—
Incidence of N+(1-3)/ER+ breast cancer (per 100,000 population)	9.74	—	19
Proportion of HER2-negative tumors	90%	—	19
Proportion with assay testing	20%	10%-60%	—
Percentage receiving chemotherapy with:			
Usual care	71%	—	8, 20
Assay testing (base case)	54% ^b	43%-60% ^c	10, 11, 13, 14, 21-25
Assay testing (age 65+)	49% ^d	—	26
Probability of completing chemotherapy regimen at specified dose	95%	—	27
Probability of chemotherapy-related:			7, 15, 28-37
Minor adverse event	85%	—	
Major adverse event	30%	—	
Fatal adverse event	0.5%	—	
Second primary cancer	2.7%	—	38
Probability of disease-related death ^e	Age specific	—	19
Probability of death from other causes ^e	Age specific	—	39

N+(1-3)/ER+ indicates node-positive, estrogen receptor-positive.

^aModel population consisted of managed care health plan members with an age distribution representative of the US population.

^bReflects a 24% reduction in chemotherapy use compared with usual care: $71\% \times [1.0 - 0.24] = 54\%$.

^cReflects a 15% to 40% reduction in chemotherapy use compared with usual care: $71\% \times [1.0 - 0.15] = 60\%$; $71\% \times [1.0 - 0.40] = 43\%$.

^dReflects a 31% reduction in chemotherapy use compared with usual care: $71\% \times [1.0 - 0.31] = 49\%$.

^eMortality estimates used in model to estimate total lifetime quality-adjusted life years lost associated with chemotherapy, chemotherapy-related supportive care and adverse events, second primary cancers, and recurrence. Age-specific all-cause mortality was based on national statistics; age- and disease-specific mortality used SEER (Surveillance Epidemiology and End Results) estimates of overall age-specific breast cancer mortality.

were based on a 2007 survey of medical oncologists in private oncology practices.²⁷

Valuing Outcomes. The numbers of annual disease diagnoses, Oncotype DX tests, and adverse events associated with each strategy were estimated as the products of event incidence and plan population estimates for each age group. The total annual numbers of events were multiplied by their associated QALYs lost and costs (Table 2) to estimate the net health and economic impact of each strategy. All QALY and cost estimates were discounted at 3% per year.

Health-Related Quality of Life. Estimates of QALYs lost associated with each episode of chemotherapy treatment were based on an analysis that evaluated the survival benefit required by a cohort of patients with early-stage breast cancer before they would be willing to have chemotherapy⁴² and on an economic analysis of targeted chemotherapy use among women with early-stage breast cancer.¹⁷ We applied 0.5 QALY

lost over the course of a lifetime for each patient who received chemotherapy, assuming that this decrement encompassed the health-related quality-of-life effects associated with all chemotherapy-related supportive care and adverse events except for chemotherapy-related second primary cancers.

We computed QALYs lost associated with secondary primary tumors and disease recurrence using a decision-analytic modeling approach, in which we incorporated disease-specific mortality, health-related quality-of-life weights, and mortality from other causes.^{19,39} On the basis of assumptions from previous economic analyses of chemotherapy use in breast cancer,^{16,17} we weighted the years of survival with a utility of 0.9 for women without recurrence or other tumor and 0.7 for those with either event, adjusted at a 3% annual discount rate and assuming a 2-year average survival time after diagnosis with recurrence or second tumor.^{45,46} We applied the resulting 9.1 QALY decrement to recurrent breast cancer as well as to

Table 2. Cost and Quality-of-Life Inputs in a Decision-Analytic Model of a 21-Gene Assay for Determining Adjuvant Chemotherapy Decisions for Early-Stage N+(1-3)/ER+ Breast Cancer^a

Variable	Base Case Estimate	Range for Sensitivity Analyses	Reference
Per patient net lifetime QALY gains associated with chemotherapy and cancer events			
Chemotherapy	-0.5	—	17, 38, 41, 42
Recurrence	-9.1	—	
Second primary cancer caused by chemotherapy	-9.1	—	
Per patient annual costs (2009 dollars)			
Assay	\$3975	—	Genomic Health, Inc.
Chemotherapy drugs and administration	\$13,360 ^a	±25%	Centers for Medicare & Medicaid Services ^b
Chemotherapy-related adverse events ^c	\$8047	±25%	17, 38
Chemotherapy-related supportive care ^d	\$4283	±25%	Centers for Medicare & Medicaid Services ^{b,43}
Distant recurrence	\$40,162	—	41, 44

QALY indicates quality-adjusted life-year.
^aModel population consisted of managed care health plan members with an age distribution representative of the US population.
^bMedicare Part B Average Sales Price + 6%, estimated as average costs among plans and not adjusted for plan discounts and member cost sharing.
^cIncludes weighted costs of minor, major, and fatal adverse events and second primary nonbreast cancers.
^dIncludes treatment with granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, erythropoietin, and antiemetics.

second primary nonbreast cancers based on assuming that this average value encapsulates the highly varying survival rates associated with such cancers. We did not assume quality-of-life or survival decrements associated with assay testing.

Costs. We estimated costs of Oncotype DX testing and direct medical costs associated with chemotherapy-related drugs and administration, adverse events, and supportive care in the treatment of primary and recurrent breast cancer and second primary cancers. The assay cost was based on a US unit price of \$3975, effective July 1, 2009. To determine per episode chemotherapy drug and administration costs, we considered treatment patterns reported by oncologists for common injectable and oral chemotherapy regimens²⁷ and each regimen’s 2008 Medicare Part B average sales price (ASP). Assuming that 95% of recommended doses would be received²⁷ and adding 6% for over-ASP costs, we estimated a final per unit chemotherapy cost of \$13,360 ($[\$13,267 \times 95\%] \times [1+6\%]$; Table 2).

Chemotherapy-related adverse event and supportive care costs per treatment episode (\$8047 and \$4283, respectively) were estimated based on per event costs from a recent economic analysis of adjuvant chemotherapy¹⁷ and on 2008 Medicare Part B ASP and were weighted by event incidence.^{7,15,27-38} We estimated costs of distant recurrence based on assumptions from published cost-effectiveness and cost-of-illness analyses.^{41,44} We defined distant recurrence costs as direct medical costs of chemotherapy drugs and administration, all visits, laboratory tests and imaging, hospitalizations,

and end-of-life care, for an estimated total cost of \$40,162. All costs were adjusted to 2009 dollars using the Consumer Price Index.⁴⁷

One-way sensitivity analyses were conducted to evaluate the impact of key model assumptions on outcomes. We varied the proportion of patients tested from 10% to 60% and the reduction in chemotherapy treatment associated with use of the assay from 15% to 40%,^{10,11,13,14,22-25} as well as all costs associated with adjuvant chemotherapy treatment (±25% of base case estimate). We also conducted an analysis for a Medicare population, for whom we applied a model start age of 72 years to represent the mean age of diagnosis and a 31% reduction in chemotherapy associated with assay testing; all other estimates (eg, disease incidence) for this scenario remained consistent with those in the base case.

RESULTS

Table 3 shows the results of the base case analysis evaluating QALYs and cost outcomes for the assay testing strategy compared with the status quo in a 2-million member plan, of whom 175 ($2,000,000 \times [9.74/100,000] \times 90\% = 175$) patients would be diagnosed with early-stage N+(1-3)/ER+ HER2-negative breast cancer and 35 ($175 \times 20\%$) would be tested annually. The model predicted that each of these women receiving the assay would, over the course of 1 year, gain 0.085 QALY from avoiding chemotherapy and 0.042 QALY from the reduc-

■ **Table 3.** Annual QALY Gains and Cost Saving Associated With Use of a 21-Gene Assay in Adjuvant Chemotherapy Decisions for Early-Stage N+(1-3)/ER+ Breast Cancer in a US Managed Care Plan (N = 2,000,000), Compared With Usual Care^{a,b}

Variable	Parameter Variations for One-Way Sensitivity Analyses							
	BC	Assay Utilization Among N+(1-3)/ER+ Patients		Reduction in Chemotherapy With Assay Testing ^c		Treatment Costs ^d		Medicare Population (31% Reduction in Chemotherapy) ^e
		Low (10%)	High (60%)	Low (15%)	High (40%)	Low: BC [-25%]	High: BC 25%	
No. of patients with N+(1-3)/ER+	175	175	175	175	175	175	175	175
No. of N+(1-3)/ER+ patients tested with <i>OncoType</i> DX	35	18	105	35	35	35	35	35
Adverse events avoided	6%	6%	6%	4%	9%	6%	6%	7%
QALYs gained with use of <i>OncoType</i> DX								
Chemotherapy related	0.085	0.085	0.085	0.053	0.142	0.085	0.085	0.111
Recurrence related ^e	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Second primary cancer related	0.042	0.042	0.042	0.026	0.070	0.042	0.042	0.014
Total per patient QALYs gained	0.127	0.127	0.127	0.080	0.212	0.127	0.127	0.125
Total population QALYs gained	4.44	2.22	13.33	2.79	7.44	4.44	4.44	4.40
Costs incurred (saved) per patient tested								
<i>OncoType</i> DX	\$3975	\$3975	\$3975	\$3975	\$3975	\$3975	\$3975	\$3975
Chemotherapy drugs	(\$2267)	(\$2267)	(\$2267)	(\$1423)	(\$3794)	(\$1700)	(\$2834)	(\$2976)
Supportive care	(\$727)	(\$727)	(\$727)	(\$456)	(\$1216)	(\$545)	(\$909)	(\$954)
Adverse events	(\$1365)	(\$1365)	(\$1365)	(\$857)	(\$2285)	(\$1024)	(\$1707)	(\$1792)
Recurrence	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Total per patient costs (saved)	(\$384)	(\$384)	(\$384)	\$1239	(\$3321)	\$706	(\$1474)	(\$1747)
Total population costs (saved)	(\$13,476)	(\$6738)	(\$40,427)	\$43,445	(\$116,445)	\$24,738	(\$51,689)	(\$61,267)
Costs per QALY gained	Cost saving with net QALY gain		\$15,578/ QALY	Cost saving with net QALY gain		\$5567/ QALY	Cost saving with net QALY gain	

BC indicates base case; N+(1-3)/ER+, node-positive, estrogen receptor-positive; QALY, quality-adjusted life-year.

^aPopulation age distribution representative of US population.

^bChemotherapy use: in usual care 71%; 24% reduction (54% rate) among women tested with *OncoType* DX.

^cPercentage reduction in chemotherapy rate from 71% in usual care; 15% reduction = 60% chemotherapy rate; 40% reduction = 43% rate; 31% reduction (Medicare) = 49% rate.

^dVaried cost parameters included costs of chemotherapy drugs, supportive care, adverse events, and recurrence. Cost of *OncoType* DX test was not varied.

^eDisease recurrence rates equivalent between usual care and testing strategies (reduction in chemotherapy among tested patients occurred in those with low recurrence risk).

tion in chemotherapy-related secondary primary tumors, for a net annual gain of 0.127 QALY per tested patient.

The testing strategy would also result in annual cost savings of \$4359 per patient tested, including \$2267 in avoided chemotherapy, \$727 in avoided supportive care, and \$1365 in avoided adverse events. With the cost of the assay included, testing would result in annual total net savings of \$384 per patient tested. For a 2-million member plan and compared with the status quo of treating 71% of eligible patients, use of the assay in treatment decisions was predicted to result in a total of 4.44 QALYs gained and \$13,476 saved each year, with savings of \$0.0006 per member per month or \$6 per eligible N+(1-3)/ER+ HER2-negative member per month.

Overall, the assay testing strategy was predicted to increase QALYs and to be cost neutral with respect to cost saving.

These results were not sensitive to changes in input estimates of the proportion of patients tested, to a greater reduction in chemotherapy associated with assay testing, or to higher costs associated with adjuvant chemotherapy treatment. In addition, QALY gains and cost savings were greatest when the rates of testing were increased, when there was a greater reduction in chemotherapy associated with assay testing, and when chemotherapy-related costs were increased.

For example, when we varied the proportion of patients tested between 10% and 60%, the predicted total plan QALYs gained ranged between 2.22 and 13.33 and total plan savings ranged between \$6738 and \$40,427, but there was no change in per patient QALY gains or costs saved. Increasing the impact of testing to a 40% reduction in chemotherapy increased net annual QALYs gained to 7.44 and cost savings

to more than \$116,000. Use of the assay was associated with any cost accrual rather than savings only when the reduction in chemotherapy associated with assay use was reduced to 15% and when chemotherapy-related costs were 25% lower than those in the base case. However, in both cases there were still QALY gains and the incremental cost-effectiveness ratios (ICERs) were low at \$15,578 and \$5567 per QALY, respectively.

When testing was limited to women 65 years and older (eg, to represent the Medicare population) and there was a 31% reduction in chemotherapy associated with assay testing, net QALY gains remained almost the same at 4.40 but cost savings more than quadrupled to \$61,267.

DISCUSSION

Interventions to improve health are often evaluated with regard to their cost and effectiveness, and most interventions require increased expenditures in exchange for improved health.⁴⁸ The cost per year of life gained for the last 4 decades of medical spending in the United States was \$30,000 to \$85,000,⁴⁹ and a frequently cited threshold value for cost-effectiveness is \$50,000 per QALY.⁵⁰⁻⁵² The incremental cost-effectiveness of the Oncotype DX assay for use in early-stage N+(1-3)/ER+ HER2-negative breast cancer appears to fall well below this level and indeed improves health while being either cost neutral or cost saving. That is, a health plan using the assay for patients with 1 to 3 positive nodes would experience improved quality outcomes among its members at essentially zero incremental cost.

Opportunities to improve health at no incremental cost are rare. A systematic review of the cost-effectiveness literature found that fewer than 1 in 5 interventions were cost saving,⁴⁸ and another analysis found that only 4 of 18 widely recommended quality measures saved money.⁵³ Our results suggest that the 21-gene assay, on the other hand, not only provides marginal cost savings to payers but also offers vital quality improvement to patients, who could avoid toxicities such as nausea and vomiting, ovarian failure, new primary tumors, or cognitive dysfunction.

The promising results of this analysis must be considered in light of its potential limitations. Our estimate of the net reduction in chemotherapy associated with assay testing is based on a single published study for the general N+(1-3)/ER+ population²¹ and on a separate analysis²⁶ for the ≥ 65 -year age group. However, these estimates are consistent with those found in studies of N-/ER+ patients, which have shown that incorporating assay results into clinical practice changed treatment decisions in 21% to 44% of cases.^{10,11,13,14,22-25} In sensitivity analyses, we evaluated results when estimated reductions in chemother-

apy were 15% (smaller than the lowest published estimate) and still found that use of the assay would be highly cost-effective.

Our model used an age distribution representative of the US population for estimating breast cancer incidence, yet we applied the model to a potentially younger managed care population.^{54,55} Our estimates of breast cancer incidence (which is higher among older persons) may thus overestimate the incidence in a managed care population for the model base case and underestimate it in the Medicare/Medicare Advantage scenario. Although this difference would cause our model to slightly overestimate total plan cost savings in the base case and underestimate them in the Medicare/Medicare Advantage scenario, it would not impact per patient results or overall conclusions of cost savings with net QALY gains.

We used a payer perspective and did not account for indirect costs (such as lost work, decreased productivity, and travel time) that may be associated with chemotherapy treatment and cancer recurrence, nor did we take into account the costs associated with oncologists' time and resource expenditures in managing chemotherapy treatment (eg, all office visits and laboratory tests during a course of chemotherapy treatment)⁵⁶ or adverse events. We also used clinical trial data to estimate costs of treatment, hospitalization, and medications associated with adverse events, yet such costs are often greater in noncontrolled settings and may have increased in recent years because of the use of more expensive treatments and technology. The results of our model may thus underestimate the total cost savings associated with 21-gene assay testing when considered from a societal perspective and can be considered a conservative estimate of the assay's cost-effectiveness in N+(1-3)/ER+ patients.⁵⁷

Finally, it has been shown elsewhere that treatment intensity was decreased among some N+(1-3)/ER+ patients with intermediate recurrent score results^{10,21}; however, we chose to model change in chemotherapy use only among those with low recurrent score results to provide a conservative estimate of the benefits gained from the assay's use in this population. When we conducted sensitivity analyses to address the impact of this assumption, decreasing the proportion of tested patients who received chemotherapy after assay testing from 54% to 42% resulted in greater population-wide QALY gains (7.44 vs 4.44) and cost savings (\$116,445 vs \$13,476). In this way, the results of our model may again underestimate the benefits associated with use of the assay.

On the other hand, it is possible that we overestimated the benefits gained when reducing chemotherapy use among patients with low recurrent scores. Specifically, a key model assumption is that there is no difference in survival for patients with low recurrent scores regardless of whether these patients received adjuvant chemotherapy. To evaluate how results

and conclusions would vary if there were a small benefit of such treatment, we conducted a one-way sensitivity analysis in which chemotherapy provided survival gains equivalent to its related QALY losses. We found with this scenario that QALY gains for the total population would decrease from 4.44 to 1.47, but our original conclusion of cost savings with net QALY gains would remain constant.

Further, we may have overestimated plan costs of chemotherapy drugs and supportive care because Medicare Part B ASP estimates do not incorporate plan discounts or member cost sharing, and we may have also overestimated the incidence of chemotherapy-related minor adverse events, the rates of which have been reported in some analyses to have been reduced in recent years.⁵⁸ However, when we tested these assumptions by decreasing costs by 25% and decreasing chemotherapy-related adverse event rates by 50%, assay testing was still predicted to be highly cost-effective (ICER <\$10,000 per QALY). We also assumed there would be no quality-of-life decrement associated with assay testing (eg, from anxiety provoked while waiting for test results or from a result indicating elevated recurrence risk). However, evidence indicates that decision anxiety is lower with routine use of the test,¹² and even if such a decrement did exist, it would likely be small and have minimal impact on our conclusions.

We used unpublished survey data to estimate practice patterns of chemotherapy-related supportive care.²⁷ We conducted one-way sensitivity analyses to specifically evaluate the impact of using such data on model results, and we found that even extreme differences in these values did not change conclusions regarding the cost-effectiveness of the assay's use in this population. Specifically, doubling the final cost input values resulted in an almost 3-fold increase in net cost savings, while halving them resulted in a positive yet small ICER of \$1364 per QALY.

We applied 0.5 cumulative QALY lost over the course of a 30-year time horizon for each patient who received chemotherapy treatment, based on published results that used time trade-off methodology to show that, on average across a cohort of 104 women who had received chemotherapy, the net survival benefit of accepting chemotherapy equaled 0.5 year. However, there is great variability in the value that patients attribute to chemotherapy treatment,^{59,60} and in fact estimates based on time trade-off methods often overestimate results because the "gained" years of life come at the end of the life span and thus would in actuality be valued less (because they are further in the future).⁶¹ Overestimating the QALY losses attributed to chemotherapy is equivalent to underestimating the utility attributed to chemotherapy, and we conducted a one-way sensitivity analysis to evaluate the impact of this assumption on model results and conclusions. When the QALY loss was reduced to as low as 0.01 cumulative QALY lost over

the lifetime, total population QALY gains decreased from 4.44 to 1.528, but the model conclusions of net QALY gains with cost savings still did not change.

We estimated that 90% of cancers would be non-HER2 overexpressing, although estimates of such cancers are changing and thus may be uncertain. To evaluate the impact of our estimate on model results, we ran the analysis when the proportion of non-HER2 overexpressing cancers was set to 80% instead of 90%. We found that lower rates of these cancers would slightly reduce total population cost savings (from \$13,476 to \$11,978) and total population QALY gains (from 4.44 to 3.95); thus, model conclusions of net QALY gains with cost savings would not change.

Similarly, our estimate of a 2.7% excess risk among patients receiving chemotherapy may be an overestimate because it is based on data that include the excess risk associated not only with chemotherapy but also with radiotherapy and hormonal treatment. When we evaluated the impact of this possible overestimate on model results and conclusions, we found that the excess risk attributed to chemotherapy alone had to be as low as 0.5% for the assay to no longer be cost saving, and even when this excess risk was as low as 0.01%, the ICER was still low at less than \$1000 per QALY gained.

Our model did not address use of the assay in the population with the current greatest use (ie, women with N-/ER+ cancers), yet its value in this population has already been demonstrated in other analyses. One model in this population predicted cost savings of more than \$300 per patient tested and average gains of 0.2 QALY compared with treatment decisions based on the 2004 NCCN guidelines.⁶² In another analysis, assay-guided decisions led to life expectancy gains and were highly cost-effective (<\$2000 per life-year saved) when compared with a tamoxifen-only strategy, and led to similar life expectancy outcomes and consistent cost savings when compared with a tamoxifen-plus-chemotherapy strategy.¹⁶ The assay was also found to be cost-effective (<\$11,000 per QALY) in Israel, where lower chemotherapy and administration costs reduce the potential savings per patient tested.¹⁸

Our model also assumed that cancer and all-cause mortality were estimated based on national statistics but did not incorporate one additional benefit of the Oncotype DX assay: once the recurrent score is known, patients' risk of cancer-related death is stratified into 3 categories based on the assay result. However, because the addition of this prognostic factor would not change model results (average risk of death would be the same across patients in both strategies), and because the model estimated *differences* in quality-adjusted survival between strategies, we chose to maximize model parsimony while maintaining clinical validity by not including this aspect of recurrent score results.

CONCLUSIONS

The use of a 21-gene reverse transcriptase polymerase chain reaction assay in patients with early-stage N+(1-3)/ER+ HER2-negative breast cancer has the potential to offer the US healthcare system significant quality improvement at no additional payer cost. Our model predicted that the substantial savings in chemotherapy-related costs would outweigh the cost of the test itself and that patients would experience substantial quality-of-life gains associated with reductions in chemotherapy.

Although real-world confirmation of these promising outcomes is needed in the N+(1-3)/ER+ population (as has already been shown among N-/ER+ patients), these results should provide insight for US health plans, the Centers for Medicare & Medicaid Services, and clinicians alike in establishing coverage policies and in making treatment decisions for women with early-stage N+(1-3)/ER+ HER2-negative breast cancer.

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Author Affiliations: From Aetna (BFV), Chicago, IL; Partnership for Health Analytic Research, LLC (MSB, EYC, TGKB), Beverly Hills, CA; and New York University School of Medicine (RO), New York, NY.

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Address correspondence to: Michael S. Broder, MD, Partnership for Health Analytic Research, 280 S Beverly Drive, Suite 404, Beverly Hills, CA 90212. E-mail: mbroder@pharllc.com.

REFERENCES

1. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med*. 1989;320(8):479-484.
2. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. *J Natl Cancer Inst*. 1997;89(22):1673-1682.
3. Fisher B, Jeong JH, Bryant J, et al; National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. *Lancet*. 2004;364(9437):858-868.
4. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24(23):3726-3734.
5. 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*. 2004;351(27):2817-2826.
6. Habel LA, Shak S, Jacobs MK, et al. A population-based study of

tumor gene expression and risk of breast cancer death among lymph node-negative patients. *Breast Cancer Res*. 2006;8(3):R25.

7. Dowsett M, Cuzick J, Wales C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol*. 2010;28(11):1829-1834.

8. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: Breast Cancer*. V.1.2010. http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. Accessed September 29, 2010.

9. Harris L, Fritsche H, Mennel R, et al; American Society of Clinical Oncology. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol*. 2007;25(33):5287-5312.

10. Lo SS, Mumby PB, Norton J, et al. Prospective multicenter study of the impact of the 21-gene recurrence score assay on medical oncologist and patient adjuvant breast cancer treatment selection. *J Clin Oncol*. 2010;28(10):1671-1676.

11. Liang H, Brufsky AM, Lembersky BB, Rastogi P, Vogel VG. A retrospective analysis of the impact of Oncotype DX low recurrence score results on treatment decisions in a single academic breast cancer center. Poster presented at: 30th Annual San Antonio Breast Cancer Symposium; December 13-16, 2007; San Antonio, TX.

12. Mumby PB, Lo SS, Norton J, et al. Prospective multi-center study of the impact of the 21-gene recurrence score assay on patient satisfaction, anxiety and decisional conflict for adjuvant breast cancer treatment selection. Poster presented at: 30th Annual San Antonio Breast Cancer Symposium; December 13-16, 2007; San Antonio, TX.

13. Erb C, Fox KR, Patel M, et al. Evaluation of practice patterns in the treatment of node-negative, hormone-receptor positive breast cancer patients with the use of the Oncotype DX assay at the University of Pennsylvania. Poster presented at: 30th Annual San Antonio Breast Cancer Symposium; December 13-16, 2007; San Antonio, TX.

14. Ben-Baruch N, Hammerman A, Klang S, Lieberman A. A prospective study of the impact of the 21-gene recurrence score assay on treatment decisions in N-, ER+ early-stage breast cancer patients. *J Clin Oncol*. 2007;25(18S): June 20 suppl).

15. Albain KS, Barlow WE, Shak S, et al; Breast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomized trial. *Lancet Oncol*. 2010;11(1):55-65.

16. Lyman GH, Cosler LE, Kuderer NM, Hornberger J. 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*. 2007;109(6):1011-1018.

17. 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 [published correction appears in *Am J Manag Care*. 2005;11(8):476]. *Am J Manag Care*. 2005;11(5):313-324.

18. Klang SH, Hammerman A, Lieberman N, Efrat N, Doberne J, Hornberger J. Economic implications of 21-gene breast cancer risk assay from the perspective of an Israeli-managed health-care organization. *Value Health*. 2010;13(4):381-387.

19. SEER: Surveillance Epidemiology and End Results Program of the National Cancer Institute. SEER*Stat Software. Version 6.4.4. <http://seer.cancer.gov/seerstat>. Published April 24, 2008. Accessed November 8, 2010.

20. Giordano SH, Hortobagyi GN, Kau SW, Theriault RL, Bondy ML. Breast cancer treatment guidelines in older women. *J Clin Oncol*. 2005;23(4):783-791.

21. Oratz R, Kim B, Chao C, et al. Physician survey of the effect of the 21-gene recurrence score assay results on treatment recommendations for patients with lymph node-positive and estrogen receptor-positive breast cancer. *J Oncol Pract*. In press.

22. Oratz R, Paul D, Cohn AL, Sedlacek SM. Impact of a commercial reference laboratory test recurrence score on decision making in early-stage breast cancer. *J Oncol Pract*. 2007;3(4):182-186.

23. Henry LR, Stojadinovic A, Swain SM, Prindiville S, Cordes R, Soballe PW. The influence of a gene expression profile on breast cancer decisions. *J Surg Oncol*. 2009;99(6):319-323.

24. Asad J, Jacobson AF, Estabrook A, et al. Does Oncotype DX recurrence score affect the management of patients with early-stage breast cancer? *Am J Surg*. 2008;196(4):527-529.

25. Thanasoulis T, Brown A, Frazier T. The role of Oncotype DX™ assay on appropriate treatment for estrogen positive, lymph node negative

invasive breast cancer. Presented at: 9th annual meeting of the American Society of Breast Surgeons; April 30-May 4, 2008; New York, NY.

26. Oratz R, Chao C, Skrzypczak S, Ory C, Broder M. Effect of 21-gene recurrence score results on treatment recommendations in patients age 65 and older with lymph node-positive, estrogen receptor-positive breast cancer [abstract e11077]. *J Clin Oncol.* 2010;28(15S, May 20 suppl).

27. Interactive Clinical Intelligence Market Research. OncoReport: Medical Oncology T3 2007. <http://www.icimrr.com/reports.html>. Accessed November 18, 2010.

28. de Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. *J Clin Oncol.* 2003;21(22):4105-4111.

29. de Wit R, Herrstedt J, Rapoport B, et al. The oral NK(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. *Eur J Cancer.* 2004;40(3):403-410.

30. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. *Cancer.* 2004;100(10):2261-2268.

31. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-responsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol.* 1990;8(9):1483-1496.

32. Herrstedt J, Apornwirat W, Shaharyar A, et al. Phase III trial of capsoptant, a novel neurokinin-1 receptor antagonist, for the prevention of nausea and vomiting in patients receiving moderately emetogenic chemotherapy. *J Clin Oncol.* 2009;27(32):5363-5369.

33. Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol.* 2005;23(16):3686-3696.

34. Martin M, Pienkowski T, Mackey J, et al; Breast Cancer International Research Group 001 Investigators. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med.* 2005;352(22):2302-2313.

35. Roché H, Yelle L, Cognetti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. *J Clin Oncol.* 2007;25(23):3415-3420.

36. Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol.* 2005;23(12):2822-2830.

37. Yeo W, Mo FK, Suen JJ, et al. A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. *Breast Cancer Res Treat.* 2009;113(3):529-535.

38. Schaapveld M, Visser O, Louwman MJ, et al. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. *J Clin Oncol.* 2008;26(8):1239-1246.

39. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. *Natl Vital Stat Rep.* 2008;56(10):1-120.

40. Seidman AD, Berry D, Cirrincione C, et al. CALGB 9840: phase III study of weekly (W) paclitaxel (P) via 1-hour (h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC [abstract 512]. *J Clin Oncol.* 2004;22(14S, July 15 suppl).

41. Garrison LP Jr, Lubeck D, Lalla D, Paton V, Dueck A, Perez EA. Cost-effectiveness analysis of trastuzumab in the adjuvant setting for treatment of HER2-positive breast cancer. *Cancer.* 2007;110(3):489-498.

42. Simes RJ, Coates AS. Patient preferences for adjuvant chemotherapy of early breast cancer: how much benefit is needed? *J Natl Cancer Inst Monogr.* 2001;(30):146-152.

43. Centers for Medicare & Medicaid Services. 2008 ASP Drug Pricing Files. http://www.cms.gov/McrPartBDrugAvgSalesPrice/01a_2008aspfiles.asp#TopOfPage. Accessed September 28, 2010.

44. Rao S, Kubisiak J, Gilden D. Cost of illness associated with metastatic breast cancer. *Breast Cancer Res Treat.* 2004;83(1):25-32.

45. Miles D, Chan A, Romieu G, et al. Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC) [abstract 41]. *Cancer Res.* 2009;69(24 suppl).

46. Waeber M, Castiglione-Gertsch M, Dietrich D, et al; Swiss Group for Clinical Cancer Research (SAKK). Adjuvant therapy after excision and radiation of isolated postmastectomy locoregional breast cancer recurrence: definitive results of a phase III randomized trial (SAKK 23/82) comparing tamoxifen with observation. *Ann Oncol.* 2003;14(8):1215-1221.

47. Katz S, Crawford M, Mauro A, eds. *CPI Detailed Report. Data for December 2009.* Bureau of Labor Statistics. <http://www.bls.gov/cpi/cpid0912.pdf>. Accessed October 26, 2010.

48. Cohen JT, Neumann PJ, Weinstein MC. Does preventive care save money? health economics and the presidential candidates. *N Engl J Med.* 2008;358(7):661-663.

49. Cutler DM, Rosen AB, Vijan S. The value of medical spending in the United States, 1960-2000. *N Engl J Med.* 2006;355(9):920-927.

50. Eichler HG, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health.* 2004;7(5):518-528.

51. King JT Jr, Tsevat J, Lave JR, Roberts MS. Willingness to pay for a quality-adjusted life year: implications for societal health care resource allocation. *Med Decis Making.* 2005;25(6):667-677.

52. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med.* 2003;163(14):1637-1641.

53. Broder MS, Yermilov I, Ko CY, Maggard MA, Ory C, Keeler EB. Does improving quality of care save money? Review of the cost effectiveness of a national set of quality indicators. Poster presented at: ISPOR 14th Annual International Meeting; May 16-20, 2009; Orlando, FL.

54. MCOL. HMO enrollment. Managed care fact sheets. <http://www.mcareol.com/factshts/factnati.htm>. Accessed November 12, 2010.

55. Banthin JS, Taylor AK. Research Findings #15: HMO Enrollment in the United States: Estimates Based On Household Reports, 1996. January 2001. Medical Expenditure Panel Survey, Agency for Healthcare Research and Quality. http://www.meps.ahrq.gov/data_files/publications/rf15/rf15.shtml. Accessed December 8, 2010.

56. Warren JL, Yabroff KR, Meekins A, Topor M, Lamont EB, Brown ML. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst.* 2008;100(12):888-897.

57. Hassett MJ, O'Malley AJ, Pakes JR, Newhouse JP, Earle CC. Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer. *J Natl Cancer Inst.* 2006;98(16):1107-1117.

58. Shih V, Wan HS, Chan A. Clinical predictors of chemotherapy-induced nausea and vomiting in breast cancer patients receiving adjuvant doxorubicin and cyclophosphamide. *Ann Pharmacother.* 2009;43(3):444-452.

59. Jansen SJ, Kievit J, Nooij MA, Stiggelbout AM. Stability of patients' preferences for chemotherapy: the impact of experience. *Med Decis Making.* 2001;21(4):295-306.

60. Love N, Ravdin P, Hortobagyi G, et al. Influence of prior therapy on breast cancer survivors' preferences for adjuvant systemic therapy in hypothetical scenarios [ASCO abstract 591]. *J Clin Oncol.* 2004;22(suppl).

61. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in Health and Medicine.* New York: Oxford University Press; 1996.

62. Hornberger J, Lyman GH, Chien R. Economic implications of 21-gene recurrence score assay: US multicenter experience [letter]. *J Clin Oncol.* 2010;28(22):e382. ■