

Economic/Societal Burden of Metastatic Breast Cancer: A US Perspective

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Breast cancer, with its high incidence and expensive treatments, puts a tremendous burden on US healthcare system resources. Excluding skin cancers, breast cancer is the most prevalent cancer among US women, with 1 in 8 women diagnosed during their lifetime.¹ Moreover, it is the second most common cause of cancer-related mortality in women (second to lung cancer).¹ In 2009, it was estimated that 192,370 women and 1910 men in the United States would be diagnosed with, and 40,610 would die as a result of breast cancer.^{1,2}

Recent years have seen annual decreases in the breast cancer incidence and death rates,¹ most likely reflecting earlier detection and better treatment. Despite these advances, the approximately 40% of patients who progress to metastatic breast cancer (MBC) can expect a median survival of only 1.5 to 3 years.^{3,4} The intent of treatment is not curative; rather, the purpose is to control the disease for as long as possible. Therapies often are complicated, intensive, and costly, especially toward the end of life; inpatient costs in the last 9 months of the terminal phase may be up to 8 times higher than in the treatment phase.⁵ The aim of this article is to address the issues that surround the economic and societal burden of MBC. The focus is on recent cost-of-illness data, with the intent of providing a context for understanding the value of the newly introduced treatments for MBC.

Drug resistance to anthracyclines and taxanes has necessitated the search for novel anticancer agents for MBC. In the last 5 years, the US Food and Drug Administration (FDA) has approved for the treatment of MBC the hormonal agents exemestane and letrozole, the targeted agents lapatinib and bevacizumab, and the cytotoxic agents gemcitabine, ixabepilone, and nab-paclitaxel (a nanoparticle albumin-bound formulation of paclitaxel). With the exception of exemestane and letrozole, which have lower drug prices, these new agents have drug prices (either average sales price or wholesale acquisition cost) in the range of \$3000 to \$8000 per month.

Costs associated with the development of new anticancer therapies continue to balloon higher with every passing year, and newer targeted agents most often are indicated in limited subpopulations of patients.⁶

To date, most targeted therapies have exhibited lackluster performance when not administered in combination with cytotoxic chemotherapy. As a result, in clinical practice, targeted

Objective: To review the issues surrounding the economic and societal burden of metastatic breast cancer to provide a context for understanding the value of newly introduced high-cost drug treatments.

Study Design and Methods: The PubMed database and relevant congress abstract databases were searched to identify cost-of-illness data with relevance to metastatic breast cancer and the cost of therapies emerging within the last 5 years.

Results: The direct costs alone have been estimated to be \$4.2 billion per year in the United States (1998 dollars), but more data are needed on the indirect and total societal costs associated with advanced disease. Of the new high-cost anticancer drugs introduced in the last 5 years, cost-effectiveness analyses have been reported only for lapatinib and ixabepilone in the United States. Both drugs showed high incremental cost-effectiveness ratios, although the estimated budget impact of ixabepilone was minimal due to expected low utilization in its approved indications. These studies did not include the broader indirect and full societal costs that could potentially be lowered by effective treatment.

Conclusions: The most current estimates of direct costs for metastatic breast cancer do not represent the full societal impact of the disease. Further research is needed to fully understand how different treatment options for metastatic breast cancer affect overall societal costs in the United States, and how outcomes in the palliative setting are valued by society.

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Take-Away Points

Lifetime direct medical costs of metastatic breast cancer (MBC) usually exceed total costs before recurrence; hospitalization and pharmaceutical costs are a significant portion of the total.

- Updated economic analysis is warranted to account for the recent approval of several costly therapies that are now available within the MBC armamentarium.
- No universal cost-effectiveness standard exists in the United States, but newer high-cost drugs for MBC are unlikely to be considered cost-effective because of their late-line indications.
- The economic value to society of these agents will likely change should they prove effective in earlier stages of breast cancer.

agents are frequently incorporated as an add-on to standard chemotherapy, rather than a replacement for standard chemotherapy, which adds to the overall cost of treatment.

Arguably, restricting use of expensive biologic therapies to their narrowly defined subpopulations and abiding by recommended indications should minimize associated budget impacts. In addition, advances in areas such as pharmacogenomics are helping to further refine the select patient populations that will experience the greatest benefit from targeted treatment. However, off-label utilization (by indication, dosing, or in off-label combinations) has been estimated to approach 50% for all oncology regimens.^{7,8} Generally speaking, it is not clinically appropriate (in terms of safety or efficacy) to extrapolate clinical trial data to support off-label use in patients who are not reasonably reflective of the studied populations. Moreover, although improved overall survival remains the gold standard for approval in first-line MBC, looming unmet medical need has resulted in newer agents being approved based on surrogate endpoints such as improvement in progression-free survival.⁹

Thus, society is burdened with ever-increasing drug costs associated with less and less evidence to support the claim of long-term benefit to the overall population patients with breast cancer. Although it often is argued that cost-effectiveness research may lower innovation, it also can be argued that lowering the bar for drug approval may indeed lead to the same result (as marginal treatments often yield large profit).

COSTS OF BREAST CANCER

A literature search of PubMed was conducted on August 1, 2009, for studies relating to costs of recurrent or MBC for the previous 5 years (ie, 2004 to June 2009). The search strategy was as follows: (“metastatic”[ti] or “recurrence”[ti] or “recurrent”[ti] or “relapse”[ti]) and breast and cancer and (“cost”[ti] or “costs”[ti] or “economic”[ti] or “economics”[ti]). The search was limited to papers published in the previous 5 years. Additionally, other important cost-of-illness studies published from 2000 onward were identified from reference

lists of relevant articles. Four relevant studies investigating the costs specifically of recurrent breast cancer or MBC in the United States were identified and are summarized in **Table 1**.^{3,5,10,11} Three were retrospective database studies, and 1 was a state-transition model applied to incidence data. Although the studies varied in the time of follow-up, the time frames were probably adequate given the short median survival after diagnosis of

MBC.^{3,4} All studies included direct costs only and were from the payer perspective (ie, Medicare or another healthcare system). Notably, the studies did not account for out-of-pocket expenses, lost wages for time off work for the patient and/or caregiver, unpaid caregiver time, or productivity losses for society. Moreover, breast cancer affects both physical and psychological aspects of quality of life, so it is all but impossible to completely characterize the resulting economic burden.

Costs for breast cancer may account for as much as 20% of the \$228.1 billion in total costs of cancer care,¹² with estimates in the United States yielding highly variable results due to differences in study methodology and the characteristics of the study populations. A review of 29 cost-of-illness studies conducted in the United States between 1985 and 2007¹³ reported that direct per-patient lifetime costs fell between \$24,000 and \$37,000 in the 5 studies that assessed the attributable costs from a payer perspective in all breast cancer populations. When the study included total rather than attributable costs, the lifetime figures were higher (\$50,000 to well over \$100,000). Across the studies, costs increased with disease severity and recurrence but were inversely related to age at diagnosis.¹³ In general, the direct costs of care were highest in the first 6 to 12 months of treatment and in the final 6 to 12 months of life.¹³

Populations With Recurrent or Metastatic Breast Cancer

In one report, the total annual medical costs for patients with MBC in the United States were estimated at \$4.2 billion (1998 dollars).³ Notably, healthcare costs in the United States have almost doubled since 1998.¹⁴ Another study estimated costs to be more than \$3 billion when considering only the attributable costs (2004 values) associated with locoregional or distant recurrence (ie, excluding background costs associated with nonrecurrent breast cancer).¹¹ Costs increased significantly with morbidity,⁵ and as reported elsewhere for breast cancer in general, costs were higher immediately after diagnosis of recurrence and in the terminal months of life than during the continuing-care phase.^{3,5,10} As is true

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Table 1. Overview of Studies on the Costs of Treatment for Women with Recurrent or Metastatic Breast Cancer (MBC) in the United States

Reference	Payer and Year of Costing	Description	Methods	Included Costs	Cost Period	Main Findings
Berkowitz et al ³	Medicare, 1998	Lifetime direct costs of MBC for the cohort of women diagnosed with breast cancer that would progress to MBC in the United States in 1994	<ul style="list-style-type: none"> •State transition and microsimulation model •Incidence, progression, and survival data from SEER and other cancer registries •Medicare payments applied to resource use derived from healthcare claims for 344 women with recurrent or MBC in a clinical care database; costs then extrapolated to an annual US cohort of women with MBC (n = 70,650) 	Hospital and professional fees, radiotherapy, chemotherapy, hormonal therapy, management and tests, drug costs, terminal care	From time of diagnosis of recurrent breast cancer or MBC	<ul style="list-style-type: none"> •Lifetime cost^a \$59,489 per patient with MBC •Total lifetime cost^a for the annual US cohort with MBC \$4.2 billion
Rao et al ⁵	Medicare, 1997–1999	Direct costs of MBC during a mean follow-up period of 16.2 months	<ul style="list-style-type: none"> •Retrospective database case-control study •Medicare program expenditure data for 397 women with incident MBC matched with 1191 noncancer patients •Stepwise multivariate regression analysis 	Inpatient hospital, skilled nursing facility, physician/professional services, outpatient hospital clinic, diagnostic testing, home healthcare, hospice care, drugs, medical equipment, transport, and supplies	Mean follow-up period of 16.2 months from the time of diagnosis of MBC	Mean total per-patient costs were \$35,164 for MBC vs \$2167 for controls (<i>P</i> < .0001)
Lamerato et al ¹⁰	HFHS, 2003	Direct costs for breast cancer with and without recurrence in women initially diagnosed with early breast cancer	<ul style="list-style-type: none"> •Retrospective database cohort study •Charges from HFHS records for 1616 women diagnosed with early breast cancer between 1996 and 2002, including 1424 with no recurrence and 192 with subsequent recurrence^b •Linear regression analysis 	Inpatient, outpatient, chemotherapy, radiotherapy (prescription drugs were excluded)	(1) 6 months before and after recurrence (2) Total time from initial diagnosis of breast cancer (median follow-up, 44.5 months)	(1) Mean total per-patient charges for 6 months postrecurrence \$45,855 vs \$10,715 prerecurrence (<i>P</i> < .001) (2) Mean total monthly per-patient charges were \$4965, \$3498, and \$2615 with MR, LR, and CR, respectively, vs \$2003 with no recurrence (<i>P</i> < .05)
Stokes et al ¹¹	Medicare, 2004	Direct costs over a 10-year period for breast cancer with and without recurrence in women aged ≥65 years initially diagnosed with nonmetastatic breast cancer	<ul style="list-style-type: none"> •Retrospective database cohort study •10,798 women aged ≥65 years diagnosed with nonmetastatic breast cancer between 1991 and 1993 were identified in the SEER-Medicare linkage database and their resource use and costs were tracked in the database until 2002; recurrence in 2674 patients^c •10-year average cumulative costs estimated with Kaplan-Meier Sample Average estimator •Nonparametric bootstrap analysis 	All care received in hospitals, physicians' offices, nursing homes, hospices, and through home health agencies in the patients' homes	10-year period from initial diagnosis of breast cancer	<ul style="list-style-type: none"> •Total expected per-patient costs were \$53,454 with MR, \$61,601 with LR, and \$61,188 with CR vs \$42,005 with no recurrence^d •Expected per-patient costs attributable to recurrence were \$7642, \$18,515, and \$20,198 for MR, LR, and CR, respectively^e

CR indicates contralateral recurrence; HFHS, Henry Ford Health System (Detroit, MI); LR, locoregional recurrence; MR, metastatic recurrence; SEER, National Cancer Institute Surveillance Epidemiology and End Results.

^aUndiscounted.

^bRecurrence included contralateral breast (16% of patients), locoregional (26% of patients), and distant (metastasis, 58%).

^cAmong 1833 patients with available data, recurrence included contralateral breast (14% of patients), locoregional (52% of patients), and distant (metastasis, 34%).

^dNo statistical comparisons between groups were reported.

^eBootstrap analysis of undiscounted costs additional to those incurred in breast cancer patients without recurrence.

for breast cancer in general, MBC medical costs decrease with increasing age at diagnosis, peaking during the initial diagnosis of metastasis and in the terminal phase.^{3,5}

In 2 studies that analyzed the different components of care, hospitalization costs accounted for around one third to one half of total costs.^{3,5} Drug acquisition costs were not differentiated from chemotherapy administration costs, and costs also excluded supportive-care medication. For patients with MBC, pharmacy costs (including chemotherapy and nonchemotherapy drugs) accounted for about 15% of total costs.⁵ However, these expenditure data were from 1997 to 1998, during a time when fluorouracil and paclitaxel were the main drugs in use. Berkowitz and colleagues reported that the combined costs for all therapeutic modalities (chemotherapy, hormonal therapy, and radiation therapy) amounted to about 12% of total costs (1998 dollars).³

Charges Before and After Recurrence

The costs associated with recurrence have been estimated by comparing prerecurrence and postrecurrence charges.¹⁰ One such study used health records to demonstrate that for patients with MBC, prerecurrence and postrecurrence per-patient charges were \$14,138 and \$57,642, respectively, in a 6-month period comparison ($P < .01$). Costs rose to \$13,560 and \$104,502, respectively, in a 12-month comparison ($P < .001$). For patients with subsequent recurrence, mean monthly charges were \$4965, compared with \$2003 in patients without recurrence ($P < .05$ after adjusting for baseline covariates). Interestingly, mean monthly charges for the metastatic recurrence group also were numerically higher than those associated with locoregional recurrence (\$3498) or contralateral recurrence (\$2615; significance not reported for either). For the mean total per-patient charge of \$175,000 (from initial diagnosis of early disease to end of follow-up), at least \$100,000 was attributable to the occurrence of metastases. The latter estimates were somewhat higher than the other MBC per-patient cost-of-illness estimates (Table 1), which may be at least partly explained by the use of charges rather than costs.

It is worth noting that many of today's newer therapies were not taken into account in these cost analyses. Increased drug cost is driving up the cost of MBC treatment more than any other factor, and older cost data do not fully capture this trend (Table 2). In addition, many of these newer agents, especially biologic agents that are indicated or utilized as add-on therapy, often are continued indefinitely until disease progression or unacceptable toxicity. Also worth mentioning is the fact that it is generally acceptable to treat MBC patients with several lines of therapy, while most patients with other malignancies are treated with fewer unique regimens.

COST-EFFECTIVENESS OF DRUG TREATMENT

Context

A search of PubMed for cost and cost-effectiveness studies conducted in the United States for high-cost drugs that have recently been approved for use in breast cancer (ie, lapatinib, bevacizumab, gemcitabine, ixabepilone) identified only 3 relevant studies: 2 relating to ixabepilone and 1 relating to lapatinib. Therefore, studies conducted in other countries were included when available.

With the decentralized financing and delivery of health-care in the United States, cost-effectiveness data are not used explicitly in decision making at the federal or state level. The cultural and political climate of the United States is traditionally more conducive to market-based solutions than to government-enforced policies regarding return on investment for medical interventions.¹⁵ However, value remains an indirect but important criterion for policy makers, and cost-effectiveness data can influence payers' coverage and reimbursement decisions.¹⁵ Other countries (eg, the United Kingdom, Australia, etc.) operate centralized systems in which cost-effectiveness data are explicitly included in decisions regarding government funding of new drugs.^{16,17} Some evidence suggests that applying such criteria for cost-effectiveness can impede patient access to new high-cost treatment modalities and/or decrease innovation around the development of new therapies.^{17,18}

Targeted Agents

A recent cost-effectiveness analysis estimated the projected lifetime clinical and economic consequences of adding lapatinib to capecitabine as second-line therapy in HER2-positive advanced breast cancer.¹⁹ The analysis modeled outcomes for a 53-year-old woman with progressive HER2-positive locally advanced or metastatic breast cancer previously treated with a minimum of an anthracycline, a taxane, and trastuzumab. The direct costs included were wholesale acquisition costs of lapatinib and capecitabine tablets, costs of treating severe diarrhea and cardiotoxicity events, monitoring test costs, costs of treatment (in 2007 US dollars) after disease progression or central nervous system metastasis, and patient time and travel.

Mean time to progression was estimated to be 6.21 months with lapatinib plus capecitabine versus 4.24 months with capecitabine alone, and mean overall survival was estimated to be 17.41 versus 15.45 months, respectively. Based on a regimen of lapatinib 1250 mg given daily for each 21-day cycle (in combination with capecitabine as indicated), the wholesale acquisition cost of lapatinib was \$2415 per cycle (\$23 per 250-

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Table 2. Average Monthly Drug Prices of Agents Used in Metastatic Breast Cancer

Antimetastatic Breast Cancer Drug and Dosage	Average Monthly (28 days) ASP (Injectable) or WAC (Oral) Drug Price, ^a \$
Bevacizumab (Avastin) 10 mg/kg every 2 weeks	8045
Ixabepilone (Ixempra) 40 mg/m ² every 3 weeks	6375
Nab-paclitaxel (Abraxane) 260 mg/m ² every 3 weeks	6250
Gemcitabine (Gemzar) 1250 mg/m ² , days 1 & 8, every 3 weeks	4250
Capecitabine (Xeloda) 1250 mg/m ² twice daily days 1-14, every 3 weeks	3800 (WAC)
Liposomal doxorubicin (Doxil) 45 mg/m ² every 4 weeks	3770
Trastuzumab (Herceptin) 2 mg/kg weekly	3630
Lapatinib (Tykerb) 1250 mg/day	3315 (WAC)
Docetaxel (Taxotere) 75 mg/m ² every 3 weeks	3290
Fulvestrant (Faslodex) 250 mg every 4 weeks	820
Toremifene (Fareston) 60 mg/day	420 (WAC)
Letrozole (Femara) 2.5 mg/day	370 (WAC)
Epirubicin 100 mg/m ² every 3 weeks	355
Anastrozole (Arimidex) 1 mg/day	350 (WAC)
Exemestane (Aromasin) 25 mg/day	315 (WAC)
Mitoxantrone 12 mg/m ² every 3 weeks	255
Vinorelbine 30 mg/m ² weekly	230
Goserelin (Zoladex) 3.6 mg every 4 weeks	205
Paclitaxel 175 mg/m ² every 3 weeks	125
Cyclophosphamide 600 mg/m ² every 3 weeks	60
Doxorubicin 60 mg/m ² every 3 weeks	45
Tamoxifen 20 mg/day	20 (WAC)
Fluorouracil 600 mg/m ² , days 1 & 8, every 4 weeks	5
Methotrexate 40 mg/m ² , days 1 & 8, every 4 weeks	5

ASP indicates average sales price; WAC, wholesale acquisition costs.
^aAssuming 70 kg/1.73 m² patient (rounded to vial size when appropriate)—ASP/WAC data current as of January 2010.

mg tablet). The average total costs per patient were \$66,499 for lapatinib plus capecitabine, compared with \$46,869 for capecitabine alone. Thus, the addition of lapatinib to capecitabine cost an additional \$19,630 and produced a gain of 0.12 quality-adjusted life-year (QALY) over capecitabine alone.

Although regulatory bodies in other countries (eg, the National Institute for Health and Clinical Excellence [NICE]) have thresholds for cost-effectiveness, no definitive threshold exists in the United States. A recent editorial by Hillner and Smith suggested that a threshold between \$140,000 and \$200,000 per QALY might be reasonable in today's values.²⁰ For lapatinib plus capecitabine versus capecitabine alone, the incremental cost-effectiveness ratio (ICER) was \$120,184 per life-year gained and \$166,113 per QALY gained. The probability of lapatinib achieving an ICER of under \$100,000 per QALY was less than 1%, and the probability of achieving an ICER under \$150,000 per QALY was less than 2%.¹⁹ These findings indicate that the addition of lapatinib to capecitabine for second-line treatment of HER2-positive advanced breast cancer is unlikely to be considered

cost-effective within the thresholds utilized by NICE, but may fall in the range suggested by Hillner and Smith.

One cost-effectiveness analysis evaluated the addition of bevacizumab to paclitaxel in first-line treatment of HER2-negative MBC in the Swiss healthcare system.²¹ Treatment with bevacizumab plus paclitaxel was estimated to result in a median progression-free survival of 11.84 months versus 5.92 months with paclitaxel alone, and the estimated median survival times were 26.74 and 25.22 months, respectively. The acquisition cost per month for bevacizumab 10 mg/kg was €5303.92 (approximately \$7374). The addition of bevacizumab to paclitaxel increased direct lifetime costs by €40,369 (approximately \$56,100) for a gain of 0.21 QALY, resulting in an ICER of €189,427 (approximately \$263,020) per QALY gained compared with paclitaxel alone (2008 dollars).²¹

Bevacizumab is indicated only for first-line treatment of MBC. No data existed to support its use in second-line treatment of MBC until recently, when the phase III RIBBON-2 trial demonstrated a statistically significant improvement in progression-free survival over placebo (7.2 vs 5.1 months; *P* =

■ **Table 3.** Estimations for the Budget Impact Analysis of Ixabepilone²⁵

Estimation	No. of Patients	Percentage
No. of patients in health plan	1,000,000	—
No. estimated to have breast cancer	8259	0.8% of study population
No. estimated to have MBC	570	6.9% of patients with breast cancer
No. with MBC estimated to be AT-p (eligible for ixabepilone combination)	97	17% of patients with MBC
No. with MBC estimated to be ATC-p (eligible for ixabepilone monotherapy)	148	26% of patients with MBC
No. with MBC estimated to be receiving other treatments (ixabepilone ineligible)	325	57% of patients with MBC
No. with AT-p MBC estimated to be receiving ixabepilone combination		
Year 1	2.02	2.09% of patients eligible for ixabepilone combination
Year 2	1.97	2.03% of patients eligible for ixabepilone combination
Year 3	1.93	2.00% of patients eligible for ixabepilone combination
No. with ATC-p MBC estimated to be receiving ixabepilone monotherapy		
Year 1	12.42	8.39% of patients eligible for ixabepilone monotherapy
Year 2	12.79	8.64% of patients eligible for ixabepilone monotherapy
Year 3	12.76	8.61% of patients eligible for ixabepilone monotherapy

AT-p indicates anthracycline/taxane pretreated; ATC-p, anthracycline/taxane/capecitabine pretreated; MBC, metastatic breast cancer.

.0072) when used in combination with standard chemotherapy in these patients.²² Even prior to this clinical evidence, however, US clinicians frequently used it off-label for pretreated MBC because of the high unmet medical need in this patient population. This scenario represented an example of a costly off-label treatment that may have driven up the costs associated with MBC previously without supporting evidence of clinical benefit. It is interesting to note that the FDA is currently reviewing the initial accelerated approval of bevacizumab for the treatment of MBC.

Cytotoxic Agents

Ixabepilone. A prospective cost-effectiveness analysis was conducted alongside the pivotal clinical trial of ixabepilone plus capecitabine versus capecitabine alone in MBC.²³ Data on medical resource use and health utilities were collected along with clinical data, and unit costs were applied.²⁴ The analysis had a healthcare system perspective and a lifetime horizon. Costs (in 2008 US dollars) included drug costs, inpatient care, outpatient physician visits, emergency department visits, home health visits, computed tomography and magnetic resonance imaging scans, and subsequent treatments.

The mean expected survival time was 1.01 years with ixabepilone plus capecitabine versus 0.84 year with capecitabine alone. The total cost of adding ixabepilone to capecitabine was \$30,900 (total costs of \$60,900 vs \$30,000 with capecitabine alone). The difference in total costs between the treatments was mainly driven by differences in drug costs, which were \$6126 per cycle for ixabepilone plus capecitabine and \$1946 per cycle for capecitabine alone. The combination of ixabepilone plus capecitabine produced a gain of 0.09 QALY (32 days) compared with capecitabine alone. Thus, the ICER was \$193,000 per life-year gained and \$359,000 per QALY gained (after discounting).²³

Importantly, although the acquisition cost of ixabepilone is high, the budget impact may be relatively low because of the small numbers of patients that can be expected to receive the drug in its approved indication. A budget impact analysis that used a 3-year time horizon modeled the annual direct pharmacy cost of ixabepilone for MBC in a hypothetical US health plan with 1 million members (payer perspective).²⁵ The estimations, used to calculate the number of patients eligible for ixabepilone therapy, are shown in **Table 3**.²⁵ It was calculated that among the 1 million people in the plan, only about 2 patients per year would receive the ixabepilone/capecitabine combination and 12 to 13

patients per year would receive ixabepilone monotherapy. The budget impact for the health plan of introducing ixabepilone was approximately \$65,000 to \$70,000 per year (2009 dollars). Spread over all 1 million health plan members, the incremental cost per person per month was less than 1 cent in each of the years (\$0.005 in year 1 and \$0.006 in years 2 and 3).²⁵ This scenario serves as an example of how restricting the use of a costly drug to indications with a high level of supporting evidence can render it a reasonable addition to a health plan budget.

Gemcitabine. A health technology assessment conducted in the United Kingdom in 2007 may provide some indicative economic data regarding addition of gemcitabine to paclitaxel.²⁶ The model included costs for consultations, drug acquisition and administration, and treatment-related toxicity. The drug acquisition cost per cycle was £1766.84 (approximately \$2810) with the gemcitabine/paclitaxel combination and £985.60 (approximately \$1567) with paclitaxel alone. The total lifetime costs for the 2 regimens were £26,202 and £16,653, respectively (approximately \$41,670 and \$26,483). Treatment with gemcitabine produced an additional 0.32 life-year and 0.16 QALY. The ICER for gemcitabine plus paclitaxel was £30,117 (approximately \$47,895) per life-year gained and £58,876 (approximately \$93,630) per QALY gained compared with paclitaxel alone.²⁶

Interpretation of Results

These cost-effectiveness analyses indicate that, by conventional standards, these recently introduced, high-cost drugs for MBC are at best only marginally cost-effective. It is noteworthy, however, that none of the analyses used a full societal perspective. Thus, in cases where a regimen has a clear clinical benefit, these cost-effectiveness analyses fail to consider the savings that could possibly be generated by the reduced adverse impact on productivity and earning potential of the patient and caregiver.¹³

It also is worth pointing out that these cost-effectiveness analyses were conducted in the palliative setting of MBC. Due to the costs of drug development, agents are rarely considered cost-effective for their initial approved indications, typically in late-line therapy. Economic values change over a product's life cycle, as has been demonstrated for trastuzumab: the overall ICER for use in both metastatic and early breast cancer over the product life cycle from 1998 to 2016 was predicted to be less than half of the ICER calculated for the initial indication of MBC.²⁷

Moreover, there is increasing recognition that the standards and thresholds applied to cost-effectiveness results may need to be different when the treatment is prolonging life in the terminal phases of a disease. In the United Kingdom, NICE has addressed this issue for treatments used in small patient populations, allowing more flexibility in the level at which such treatments can be deemed cost-effective.²⁸ Andrew Dil-

lon, NICE Chief Executive, has said that the changes reflect the Institute's awareness that "patients, and the public, place considerable value on treatments which offer the possibility of extending life when we are close to death. We believe that we should reflect that view when we are asked to make recommendations on the use of medicines that are designed to extend life, at the end of life."²⁹ NICE has recently increased the £20,000-£30,000 (US \$31,000-\$46,000) per QALY gained threshold for certain end-of-life treatments, although it is unclear what this new maximum is at this time.

DISCUSSION AND CONCLUSIONS

Increasing costs for treatment of cancer potentially affect society as a whole. When federally funded or state-funded plans (eg, Medicare, Medicaid) carry the cost of high-priced drugs, these increased costs may ultimately be passed on to consumers as higher income taxes. Similarly, private health insurance companies' coverage of high-cost drugs may increase premiums, copayments, and deductibles across the board, not just for subscribers with cancer. It is thus imperative to understand how high-cost drugs affect the overall societal costs of cancer. Is a drug's acquisition cost outweighed by savings in other sectors of the healthcare system, or by increased productivity as a result of more effective treatment?

There are currently few cost-effectiveness analyses of the cytotoxic and targeted drugs introduced for the treatment of MBC in the last 5 years. Both lapatinib¹⁹ and ixabepilone²³ were found to have high ICER values (meaning that costs were significantly higher with minimal additional benefit over standard therapy), although the budget impact of ixabepilone was found to be minimal if it is used for on-label indications. These studies did not include the full range of medical, nonmedical, and indirect costs that could be affected by treatment. In particular, it is not known whether these drugs reduce societal productivity losses related to morbidity and mortality. The studies were conducted in heavily pretreated and/or resistant MBC populations—patients who have few treatment options, poor prognosis, and particularly high costs of treatment.

As mentioned previously, if new drugs prove to be effective in earlier stages of breast cancer, they may be more cost-effective, given that effective initial treatment can reduce the risk of costly recurrences. Newer drugs are likely to undergo additional scrutiny as they move into earlier lines of therapy. They may be required to demonstrate cost-effectiveness compared with the existing standards of care.

Although no set thresholds for cost-effectiveness exist in the United States, the American Society of Clinical Oncology has created a Cost of Care Task Force and set forth guidelines regarding the cost of cancer care.³⁰ Growing trends such as com-

parative effectiveness research also may aid in evaluating which costly oncology therapies will be worth the price. The National Comprehensive Cancer Network has recently created a white paper around comparative effectiveness research in cancer and the Institute of Medicine's (Initial National Priorities for Comparative Effectiveness Research) include several oncology-related initiatives. In addition, when cost is being discussed, it is appropriate to consider, when possible, the true episodic cost over the drug/treatment price alone. Episodic cost allows clinicians and policy makers to take a global look at differences in cost as influenced by other factors (eg, toxicities, concomitant treatments, site of service). There is a great opportunity to improve the availability of these data in the future.

Although newer agents for MBC have not significantly increased overall survival in clinical trials, the value patients and the public place on treatments that may prolong life during the final months differs from the value they place on treatments provided in other stages of disease. This suggests that traditional thresholds for cost-effectiveness, measured in costs per QALY gained, may benefit from reevaluation for patients with MBC receiving palliative therapy. In the end, however, it may prove impossible to reconcile clinical trial outcomes and society's emotional need for extended end-of-life care.

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