Economic Evaluations of Medical Care Interventions for Cancer Patients: How, Why, and What Does it Mean?

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ABSTRACT While the past decade has seen the development of multiple new interventions to diagnose and treat cancer, as well as to improve the quality of life for cancer patients, many of these interventions have substantial costs. This has resulted in increased scrutiny of the costs of care for cancer, as well as the costs relative to the benefits for cancer treatments. It is important for oncologists and other members of the cancer community to consider and understand how economic evaluations of cancer interventions are performed and to be able to use and critique these evaluations. This review discusses the components, main types, and analytic issues of health economic evaluations using studies of cancer interventions as examples. We also highlight limitations of these economic evaluations and discuss why members of the cancer community should care about economic analyses. (CA Cancer J Clin 2008;58:231–244.)

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INTRODUCTION

New medical interventions can substantially improve health outcomes but often at considerable cost to the health care system and to patients. In order to efficiently use limited health care resources, beyond the standard evaluations of safety and efficacy, it is necessary to also evaluate the relative costs and benefits (ie, cost-effectiveness) of new medical technologies.1–3 In cancer care, new technologies have included innovative interventions in cancer screening and diagnosis; medications; surgery; radiation therapy; and a wide range of ancillary, supportive, and palliative care services. Novel interventions have brought significant improvement to survival and quality of life for individuals with cancer. However, such improvement can come at a substantial cost.4 Examples of interventions that may improve outcomes for specific populations but result in increased costs include $1,000 per contrast-enhanced magnetic resonance imaging screening, which is 10 times the cost of screening mammography, in breast cancer5; $1,800 per positron-emission tomography scan for cancer staging6; $48,000 per patient per year for the use of intensity-modulated radiation therapy to treat prostate cancer7; $50,000 per patient per year for trastuzumab (Herceptin) in the treatment of HER-2–positive breast cancer8; $1,800 per month for gefitinib (Iressa) for the treatment of lung cancer4; and more than $8,000 for a 6-day course of palifermin (Kepivance) in the treatment of oral mucositis.9 Motivated by the high costs associated with new biologic agents in cancer care, a recent editorial in the Journal of Clinical Oncology called for an increasing role of economic evaluation in oncology practice.8

Economic evaluation encompasses a collection of methods that assess the costs and consequences of comparative health care interventions.10 Evaluating the health and economic impacts of these interventions has been a topic of longstanding interest among clinicians,11 and such evaluation involves a variety of issues, methods, and policy implications. For this review, we will discuss the main types of economic evaluation used to assess health care interventions.
in oncology, using published studies as examples to demonstrate how economic evaluation has been used for cancer care strategies. We will also discuss challenges in the practical application of economic evaluation and related policy implications. This review is designed for clinicians caring for individuals with cancer to assist with understanding and evaluating published economic analyses, as well as with identifying the key costs and benefits associated with their own clinical practices.

**BASIC COMPONENTS OF HEALTH ECONOMIC EVALUATIONS**

**Study Perspective and Comparators**

A well-designed health economic evaluation must clearly state the study perspective and the competing interventions to be explored. The study perspective indicates the viewpoint from which the study is conducted, which is usually that of the key decision makers, and may include society, third-party payers, patients, employers, or health care providers, among others. According to the US Panel on Cost-Effectiveness in Health and Medicine, economic evaluation taking the societal perspective should include all the costs and consequences of health care interventions no matter to whom they accrue. Although the societal perspective is recommended in most textbooks of economic evaluation, it is generally agreed that the choice of perspective depends on the purpose of the evaluation. For example, while government decision makers may be interested in costs and benefits of a new intervention to society overall, the CEO of a health care system or managed care organization is likely to be more interested in the costs and benefits that would be associated with patients in their system or organization. Payers (including Medicare) are likely to be more interested in costs that accrue to their systems rather than in overall societal costs.

Economic evaluation is almost always structured to compare one intervention with a competing alternative or alternatives. In most cases, the “standard of care” is chosen as the comparator for new interventions; for conditions that lack effective treatments, “do nothing” may represent the standard of care. Naturally, advances in technology lead to changes in the standard of care. Examples can be found in studies comparing the cost-effectiveness of chemotherapy agents. For example, earlier economic evaluation studies comparing the cost-effectiveness of treatment options for non-small-cell lung cancer (NSCLC) often chose best supportive care as the standard of care, whereas more recent studies have often used cisplatin-based regimens as the standard of care for NSCLC.

**Costs**

Costs can be broadly categorized into direct and indirect costs. Direct costs quantify resources consumed (medical and nonmedical) that are directly related to the medical interventions, whereas indirect costs (also known as productivity loss) quantify the time consumed or saved by patients and their caregivers as a result of the interventions. Indirect costs are sometimes extended to measure the long-term labor market consequences of illnesses or interventions; under these circumstances, indirect costs are further divided into morbidity costs (ie, productivity loss due to the illness) and mortality costs (ie, productivity loss due to premature death). The type of costs to be included in the analysis depends on the study perspective and purpose. Studies taking a societal perspective require the inclusion of both direct and indirect costs to capture the full economic impact of new interventions, whereas studies taking payers’ (eg, health plans) perspectives often exclude indirect costs, as payers’ primary concern is the financial burden to their health insurance plans. Employers may be more interested in indirect costs (absenteeism and lost productivity) than direct costs, as financial burden associated with indirect costs can be substantially larger than direct costs. Furthermore, whose costs will be counted may also differ by study perspective. For example, costs for patients and their caregivers are likely to be included in evaluations with a societal perspective, while a health plan might include caregiver costs only if the caregiver was also enrolled in the plan (as caregivers may have increased medical care utilization and costs compared with those not providing care to individuals with serious conditions).
Readers have found the cost terminology confusing. The term “indirect costs” is particularly confusing because it is often mistaken as overhead costs (ie, costs of doing business that are not directly associated with providing a good or service, such as insurance, rent, and lighting). Some have suggested the use of different terms to distinguish between time costs related to the receipt of treatment and productivity loss associated with morbidity and mortality, while others choose to avoid using these terms completely. No agreement has been reached to date; therefore, it is recommended that researchers clearly state what each type of cost includes in their studies.

**Time**

There are 2 ways in which the effects of time are included in economic evaluation: discounting and inflation. For studies evaluating costs of a period longer than 1 year, such as those that follow patients from treatment initiation to death, future costs and outcomes must be “discounted.” Discounting adjusts for differences in preferences (for health and money) over time; for example, most people would rather have $100 today than $100 next year because the $100 today could be used immediately or could be put in a bank, earn interest, and be worth more than $100 next year. Similarly, individuals tend to put increased value on being healthy now versus being healthy in the future. This may have important implications for preventive care; for example, individuals may value having cash now rather than paying for a cancer screening that would result in better health outcomes (from earlier-stage disease detection) in the future. It should be noted that in studies that measure costs and outcomes in different units, as in cost-effectiveness and cost-utility analyses (discussed subsequently), the general recommendation is to discount costs as well as outcomes. However, it is important to note that discounting both costs and outcomes may lead to less favorable cost-effectiveness measures for interventions with immediate costs but health benefits occurring years or decades in the future, such as vaccination, smoking cessation, and other forms of preventive care.

Time also factors into economic evaluation for inflation adjustment (that is, making sure that all costs included in an evaluation represent values from the same year). If an evaluation uses cost data from different years (eg, chemotherapy costs based on 2006 US dollars and hospital costs based on 2003 dollars), researchers will apply appropriate price indices (such as the Medical Care Component of Consumer Price Index) to “normalize” these cost values to the same year.

**Types of Economic Evaluation**

There are 6 main types of economic evaluation: cost, cost minimization, cost benefit, cost-effectiveness, cost utility, and budget impact analysis (BIA). The selection of a type of economic evaluation depends primarily on the question to be addressed but may also be influenced by factors such as data availability or target audience. Subsequently, we discuss types of economic evaluation and the criteria used to select each. We also provide examples seen in published cancer studies.

**Cost Analysis**

Cost analysis only deals with the cost component of competing interventions, regardless of potential differences in the corresponding clinical outcomes; for example, is it cheaper to treat patients with Drug A or Drug B? As this does not include differences in outcomes (eg, survival rates) between Drugs A and B, it is considered a partial form of economic evaluation. Cost analysis is often conducted to explore the economic impact of a new intervention (compared with an existing intervention) or the economic burden associated with a specific disease or condition; cost-of-illness analysis is a form of the latter type of evaluation. Results of cost analyses can be presented either in terms of the “total” or “incremental” (additional) costs associated with interventions or diseases. The latter approach involves comparing costs between 2 scenarios, one with the intervention (or condition) and the other without.

The estimated total cost of cancer in the United States, as published annually by the National Institutes of Health, is an example of
reporting total costs in cost analysis. The National Institutes of Health estimated that the total cost of cancer was $206.3 billion in 2006; of that, $78.2 billion was in direct medical costs, and $128.1 billion was in indirect costs, including $17.9 billion in morbidity costs and $110.2 billion in mortality costs. An example of a cost analysis that reports “incremental” costs can be found in the study by Shih et al in which the authors estimated the costs associated with uncontrolled chemotherapy-induced nausea and vomiting (CINV) for cancer patients of working age whose chemotherapy regimens contained at least one highly or moderately emetogenic agent. The estimated average monthly medical cost for a patient with uncontrolled CINV was approximately $1,300 higher than that for a patient whose symptoms of CINV had been controlled. A subgroup analysis in that study concluded that indirect costs per patient per month were $433 higher for those in the uncontrolled CINV group. Another example is a cost evaluation of including palifermin for the treatment of oral mucositis among patients undergoing autologous hematopoietic stem cell transplantation. Based on clinical trials data indicating that palifermin reduced the duration and frequency of oral mucositis in this patient population (compared with placebo), the authors concluded that palifermin prophylaxis was associated with a (non-significant) mean savings of $3,595 per patient.

Cost-minimization Analysis

Cost-minimization analysis (CMA) is a method of economic evaluation that chooses the least expensive alternative when the interventions under investigation have been shown to have equivalent clinical outcomes. In this type of analysis, because the clinical outcomes of all included interventions are equivalent, costs become the focus of evaluation. An example of CMA can be found in the study by Avritscher et al in which the authors compare the use of low-molecular-weight heparin and unfractionated heparin in the treatment of hospitalized cancer patients with deep venous thrombosis. The choice of CMA is justified in this study, as previous clinical study had shown low-molecular-weight heparin and unfractionated heparin to have equivalent efficacy and safety in the management of deep venous thrombosis. In another example, a Southwest Oncology Group trial comparing the use of vinorelbine plus cisplatin versus paclitaxel plus carboplatin in the treatment of advanced NSCLC found no statistically significant difference in survival or quality of life between the treatment arms. The authors, therefore, performed CMA and reported a substantially higher cost associated with paclitaxel and carboplatin combination therapy.

Cost-benefit Analysis

Cost-benefit analysis (CBA) is an evaluation method that quantifies both costs and outcomes of competing health care interventions in monetary units. The net benefit can then be calculated by subtracting the costs of an intervention (in dollars) from the value of outcomes of the intervention (also in dollars). In this form of CBA, an intervention is worth implementing if the net benefit (outcomes minus costs) is positive; among interventions with positive net benefit, the one with the largest net benefit will be selected. An alternate approach to CBA is to divide the intervention outcomes (in dollars) by the intervention costs. This ratio, known as the benefit-cost ratio, measures dollars saved for every dollar spent on an intervention; interventions with the benefit-cost ratio greater than 1 are considered to be worth implementing. Halpern et al modeled the costs of workplace-based smoking cessation programs for a cohort of 10,000 employees. For a manufacturing facility in the southern United States, over 10 years the smoking cessation program would cost $1,193,322. However, combining medical care savings and workplace (indirect cost) savings, the program is projected to save $2,575,511 over 10 years. Thus, the program yields $2,575,511 divided by $1,193,322 or approximately $2.16 in savings for every dollar spent on cessation. With a benefit-cost ratio greater than 1, the authors recommended implementing the smoking cessation program. In performing comparisons, the interventions with the maximal benefit-cost ratios are, in many cases, the same interventions that result in the maximum net benefits. However, many researchers suggest caution in the use of...
benefit-cost ratios, as their values are sensitive to how (in economic terms) the benefits and costs are designated. For example, in evaluating a new chemotherapy, supportive care costs associated with chemotherapy-induced adverse events may be considered part of the overall treatment “cost” in a benefit-cost ratio since the supportive care is part of the treatment received. However, adverse events can also be thought of as negative outcomes and thus could be considered a negative part of the “benefit” in the benefit-cost ratio. In calculating the net economic impact of a supportive care intervention, it does not matter whether a positive cost or negative benefit is included; the net result is the same. However, in determining a benefit-cost ratio, results will differ depending on whether the intervention’s costs are classified as positive costs or negative benefits.

By placing both costs and consequences in monetary units, CBA allows direct comparisons among interventions with different objectives and thus is attractive to policy makers who often need to choose among a wide array of interventions or treatment programs of varying natures (including both health care and nonhealth care programs). A somewhat controversial aspect of CBA is that it assigns explicit monetary values for each year of life, generally based on labor market values (ie, wages) for productivity (known as the human-capital approach). That is, the economic value of a year of life is based on the wages a person would earn during that year. Shibley et al used this approach to perform a CBA to estimate the economic value of cisplatin-based combination chemotherapy in the treatment of patients with advanced-stage testicular cancer. The CBA showed a net benefit of $150 million. Many researchers have challenged the use of wages to measure the value of human lives and have also raised concerns about the monetary values that are used to represent the productivity of persons not in the labor force, such as children, stay-at-home parents, or retirees.

The willingness-to-pay (WTP) approach is an alternative method to define the economic value for an intervention or a year of life. In a WTP analysis, study participants are provided with information about a real or hypothetical intervention, including its potential to increase life expectancy. Participants are then asked to specify the maximum amount of money they would be willing to pay for the intervention. The net benefit associated with the new intervention is then calculated by subtracting its actual cost from its value as determined based on the WTP responses. Leighl et al conducted a WTP study to evaluate use of oral epidermal growth factor receptor tyrosine kinase inhibitors for patients with advanced NSCLC in Canada. These investigators reported that both NSCLC patients and healthy subjects were willing to pay more for these agents but were willing to pay only a small proportion of their market price. Other examples of WTP evaluations in oncology include assessments of recombinant erythropoietin therapy for anemia among patients receiving chemotherapy.

Cost-effectiveness Analysis

Unlike CBA, which uses monetary units to measure both costs and consequences, cost-effectiveness analysis (CEA) expresses the consequences (ie, effectiveness, benefits, or outcomes) of the interventions in a nonmonetary, natural unit that is most appropriate to describe the desired objective of the interventions. These outcomes can include survival, progression-free survival, rate of complete response, or number of adverse events avoided during cancer therapy. CEA, therefore, compares interventions along 2 separate dimensions: costs and effectiveness. In cancer therapy, many new interventions are both more costly and more effective than older or “standard-of-care” interventions. For CEA, the difference in mean cost between the 2 interventions (new cost minus old cost) is divided by the difference in mean effectiveness (eg, new survival rate minus old survival rate) to get an incremental cost-effectiveness ratio (ICER). This ratio indicates the additional cost for obtaining one additional unit of outcome (eg, 1 month increase in survival or 1 additional year of life) for the new intervention compared with the old intervention. The ICER is often then compared with some selected threshold value to determine whether the new intervention is considered cost-effective. If the ICER is lower than the threshold value (ie, the incremental cost per outcome
of the new intervention is less than the accepted standard), the intervention is considered cost-effective.\textsuperscript{10,12–15}

However, in some cases new interventions are not more costly and more effective than old interventions. If a new intervention is less costly and more effective (the ideal case), then the new intervention is said to dominate its comparator(s)—that is, it produces better outcomes for less money. If, on the other hand, a new intervention is found to be more costly and yet less effective (the worst possible case), then the new intervention is dominated by its comparator(s)—it produces worse outcomes at a higher cost and, therefore, is not likely to be of interest. It is also possible for a new intervention to be both less effective and less costly than the standard of care (ie, produce less health benefit than the standard of care but at a lower cost). With net negative impacts on both costs and effectiveness, the new intervention in this case would produce a positive ICER compared with the standard of care (in the opposite manner that an intervention with greater costs and improved outcomes results in a positive ICER). There is disagreement as to whether a positive ICER produced by a better and more costly intervention is equivalent to a positive ICER from a less effective and less expensive intervention; some researchers have argued that a different (lower) threshold value should be applied to ICER derived from the latter scenario.\textsuperscript{32,33} However, the authors of this review feel that the term cost-effective should only be applied to interventions that have greater costs and greater effectiveness than the base-case intervention to avoid confusion regarding the meaning of “cost-effective.”

It is important to note that some analyses have produced values called “cost-effectiveness ratios” by dividing the cost of a single intervention (without including a comparator) by its effectiveness. These are not ICER in that they do not explicitly compare one treatment option with another. In this case, by simply dividing an intervention’s cost by its effectiveness, an assumption is made that in comparison no intervention (ie, doing nothing) has zero cost and zero effectiveness; in many cases, this clearly is not true. These ratios of cost divided by effectiveness for a single intervention therefore cannot be accurately interpreted and are not useful in economic evaluation.

An example of CEA applied to oncology is seen in a recently published study by Ng et al using data from a clinical trial of adjuvant vinorelbine plus cisplatin compared with observation after resection of stages IB–II NSCLC.\textsuperscript{34} Direct medical resource utilization data were collected from clinical trial and medical records of patients; effectiveness was measured in terms of survival (life years). Survival and costs (in 2005 Canadian dollars [$CAD]) were presented both with and without discounting at 5% per year. As expected, adjuvant chemotherapy resulted in greater costs; the mean costs of treatment per patient in the observation and adjuvant chemotherapy arms were $23,878 and $31,319, respectively. However, adjuvant therapy in the clinical trial was associated with an increase in mean survival of 12.5 months. The ICER of adjuvant chemotherapy to observation is therefore CAD$7,175 per life year gain using 5% discounted values and CAD$10,096/life year gain undiscounted. The authors conclude that adjuvant therapy for this patient population is highly cost-effective.

Although CEA allows direct comparisons between interventions with the same outcome measure, this method has drawn criticism on 2 grounds. First, decision makers cannot use results from a CEA to compare various interventions if the effectiveness units (the outcome assessed in the evaluation) differ across studies. For example, some studies may summarize the CEA results in terms of costs per life year saved, while others may report costs per additional complete response achieved. Second, CEA comparisons of 2 interventions with the same effectiveness may not fully capture qualitative differences between the interventions. For example, 2 chemotherapy regimens may produce the same survival benefit, but patients will likely prefer the regimen with fewer side effects. However, such quality-of-life differences are not explicitly incorporated in a CEA using “life year saved” as the effectiveness measure.

Cost-utility Analysis

Cost-utility analysis (CUA) is an extension of CEA that uses an effectiveness measure known
as the quality-adjusted life year (QALY) to address the limitations of CEA discussed previously. QALY is, as the name suggests, survival time (life years) weighted by the perceived quality of (or preference for) the level of health during that time. The weights used to calculate QALY, called utilities, range from 0 (immediate death) to 1.0 (perfect health). For example, assume that the median survival for a particular type of cancer among patients receiving treatment A is 2 years and is 2.5 years for those receiving treatment B. However, treatment B is associated with many more side effects and requires more frequent medical care interactions and hospitalizations, and patients receiving treatment B generally feel much sicker. The utility for patients receiving treatment A is 0.8, while for treatment B it is 0.6. QALY resulting from treatment A, on average, is 2 years times 0.8, which equals 1.6 QALY. For treatment B, QALY is 2.5 years times 0.6 or 1.5 QALY. Thus, treatment A provides better outcomes using QALY, despite involving shorter survival.

Utility weights used to calculate QALY can be collected from patients or from the general public. Although published guidelines for economic evaluations often recommend use of utilities collected from the general public (ie, a societal perspective), they also acknowledge that utilities collected from patients are appropriate.15 Utilities (health-state weights) can be collected using a number of choice-based methods that often require face-to-face patient contact.12–15,35,36 Due to practical considerations, researchers sometimes have patients complete specifically designed survey instruments, such as the EuroQol-5D questionnaire or the Health Utilities Index, and then apply published algorithms to convert data from these questionnaires to utilities.37–39

Similar to the CEA, in CUA the difference in costs between 2 interventions is divided by the difference in their QALY to produce a summary incremental cost-utility ratio, the additional costs required to achieve an additional QALY. A threshold value commonly cited in the literature of CUA is $50,000/QALY.40,41; that is, interventions that have an incremental cost of no more than $50,000 per QALY gained are considered to be cost-effective. This threshold ($50,000/QALY) was based on the annual cost (approximately $50,000) for dialysis; as Medicare provides insurance coverage for patients with end-stage renal disease (regardless of age), this value may represent the societal willingness to pay per year (or more conservatively, per QALY).42 However, Ubel et al argued that the commonly cited cost-effectiveness thresholds, ranging from $50,000/QALY to $100,000/QALY, were based on 1982 dollars; thus, these threshold values may be too low for current cost-effectiveness studies.43 In fact, higher threshold values (as high as $300,000 per QALY) have been cited in some oncology studies.43–45

A related approach that has been used to justify the economic value of new interventions is to compare the ICER for a new intervention with the published values of ICER for other accepted interventions in similar disease areas or therapeutic classes.10 Lists of ICER are available for comparison in references called “league tables.” This league-table approach is favored by some researchers because it allows comparison of health care interventions by their relative cost-effectiveness, in contrast to an arbitrarily determined threshold value. Advocates of the league-table approach argue that this allows researchers to place their findings of CEA/ CUA in a broader context and may assist policy makers in allocating health care resources amongst interventions targeted at different diseases.46 However, Drummond et al cautioned against the use of the league table because ICER across studies may not be directly comparable due to variations in methodologies.47 The values of ICER in league tables are likely to be sensitive to factors such as discount rate, method to solicit preferences, definition of costs, and the choice of study comparator or study population, which can vary widely across studies.47,48

The oncology literature provides ample examples of CUA conducted in the last decade, and Earle and colleagues have provided a comprehensive overview of earlier CUA in oncology.40 We have included 2 recently published studies as examples of CUA.49,50 In the first study, Wolowacz and colleagues compared docetaxel, doxorubicin, and cyclophosphamide (TAC) with fluorouracil, doxorubicin, and cyclophosphamide (FAC) for patients with early node-positive breast
cancer. In this study, utilities were collected from 2 sources: patients in a clinical trial that compared TAC and FAC as adjuvant therapy for women with node-positive early breast cancer in England and published literature. While TAC was associated with greater cost, it was also associated with improved QALY compared with FAC; the authors reported an ICER of £18,188 per QALY for TAC versus FAC and concluded that TAC is more cost-effective.49 A separate analysis by Kurian et al compared 3 treatment strategies for early-stage HER2/neu-positive breast cancer: no adjuvant trastuzumab, adjuvant trastuzumab therapy with anthracyclines (AAT), and adjuvant trastuzumab therapy without anthracyclines (NAT). AAT resulted in greater costs than no adjuvant trastuzumab but lower costs than NAT. Using previously published utility values, the authors reported a favorable ICER (less than $40,000 per QALY) for AAT compared with no adjuvant trastuzumab. The comparison between AAT and NAT indicated that AAT was the dominating strategy because it had lower costs and greater QALY than NAT.50

BIA

BIA has emerged more recently to address the issue of affordability, a critical and practical concern for health policy makers that may not always align with policy recommendations based on CEA or CUA.51 A growing number of payers, especially those under national health insurance systems, have started requesting BIA in addition to a CEA/CUA to assist decision makers in determining whether the cost of a new technology recommended by a CEA/CUA might “break the bank” (ie, exceed available funds), even if the new interventions under consideration are cost-effective.52 If a new intervention was found to be cost-effective but resulted in a substantial financial burden, payers may elect to decline coverage as the intervention would be unaffordable. Researchers in the field of economic evaluation had paid little attention to methodological development of BIA in the past. However, the increasing demand from payers for evidence of BIA in parallel to CEA has motivated a recent publication of good research practices for BIA.51,52

A number of countries (eg, Canada, England, France, and Poland) and professional associations in the United States (eg, Academy of Managed Care Pharmacy) also include BIA in their published guidelines for economic evaluation.52 In BIA, benefits of health care interventions are not presented explicitly but are incorporated through changes in the overall treatment costs as a result of these interventions, similar to the way that cost offsets are captured in cost analysis. However, there are 2 important differences between BIA and cost analysis. First, while cost analysis compares the costs between interventions, BIA compares the costs between 2 scenarios defined by sets of interventions: a scenario consisting of a mix of existing interventions versus a scenario that also includes the new intervention. Second, BIA incorporates changes in the size of the population seeking treatment, a phenomenon known as “induced demand,” and the substitution between current and new interventions when new interventions became available. In addition, the proportion of patients receiving each intervention is likely to vary over time.

There is little information on oncology-related BIA in the literature, partly due to the relative newness of this type of analysis but also because many such studies were submitted directly from pharmaceutical companies to the payers instead of to peer-reviewed journals.53 Hind et al has provided one of few oncology-related economic evaluations that contain a BIA. In that study, the authors assessed the economic value of hormonal therapies for early breast cancer, comparing the budget impact between paying for 5 years of tamoxifen therapy for 100% of breast cancer patients versus paying for 5 years of aromatase inhibitors for those same patients. They concluded that the budget impact would increase from £56.8 million in 2006 to £113.8 million in 2010.54

LIMITATIONS AND CHALLENGES IN APPLYING ECONOMIC ANALYSES IN ONCOLOGY

While the methods of health care economic analysis are generally well accepted, there are a number of challenges in applying economic analysis to oncology. First, many newer medical
interventions, such as those being used as second, third, or later-line therapy for metastatic disease, may have substantial costs but produce relatively small increases in outcomes. For example, a 3-month (0.25 years) increase in survival for metastatic cancer is significant clinically, but if it comes at a cost of tens of thousands of dollars per patient, it is unlikely to be considered cost-effective. Further, this 0.25 life year increase is likely to be associated with symptoms related to both the new therapy and the underlying cancer and thus will result in an increase in QALY of less than 0.25, leading to less likelihood of achieving cost-effectiveness. Another example involves medications that prevent chemotherapy-related side effects. Newer medications can be substantially more expensive than older drugs, and while the newer medications may be more effective (eg, in preventing nausea and vomiting), their impact is only for the relatively brief period during which active therapy is ongoing. As there is only a short period for which a new (and more expensive) drug that is better in preventing nausea can improve quality of life, the net quality-of-life impact is smaller than that for therapies having long-term impacts (eg, treatments that increase life expectancy by years). The cost-effectiveness of ondansetron versus metoclopramide to prevent nausea and vomiting in a cohort of patients receiving high-dose cisplatin therapy was estimated as $407,667/QALY. This does not necessarily mean that expenditures to increase life expectancy of patients with metastatic disease or decrease treatment-related side effects are not “worth the cost”; many individuals in the cancer community and the general public would likely feel that these are important health investments. However, this has led some researchers to conclude that the current methods and decision criteria used in CEA/CUA may not be appropriate, especially for supportive/palliative care products, and to call for better methods to assess the economic value of such interventions.

Second, data for cancer-related economic evaluation (particularly effectiveness measures) are often obtained from clinical trials. However, characteristics of clinical trial participants may differ substantially from those of the “average” cancer patient, and thus cost-effectiveness analyses based on trial data may not correspond to real-world values. In particular, since the mix of real-world cancer patients is likely to be older and include a larger proportion of individuals with significant comorbidities than that of clinical trial patients, economic analyses based on trials may not be fully generalizable.

Third, many studies of economic evaluation are performed using a societal perspective, including all direct and indirect costs that are influenced by the disease and intervention. While such societal analyses may be appropriate for broader resource-allocation decisions, they may not be as useful for clinicians, health care systems, payers, and patients. Similarly, utilities used to calculate QALY are often collected from the general population. However, for clinical decision making, utilities collected from patients are probably more relevant. Thus, economic analyses that attempt to be broad enough to demonstrate costs and benefits for large groups of society may not provide information that is specific enough for a given patient or clinician.

Lastly, there is often a disconnect between evidence supported by economic evaluation and the observed practice patterns in the United States. For example, in spite of a lack of economic evidence to support the use of paclitaxel + carboplatin (versus vinorelbine + cisplatin) in the treatment of advanced NCSLC in a published CMA study, the paclitaxel-based regimen was still used extensively in clinical settings. Economic evaluation has become an integral part of the coverage and reimbursement decisions for adopting new health care interventions in Australia, Canada, and many European countries. These countries have created government-funded agencies, such as the National Institute for Health and Clinical Excellence in the United Kingdom, Common Drug Review in Canada, and the Pharmaceutical Benefits Advisory Committee in Australia, to review or generate information on economic evaluation and to make recommendations to reimbursement authorities. To date, the US government has not formally endorsed the use of economic evaluation in coverage and reimbursement decisions. There had been sporadic interest in a more official role of economic evaluation for the Medicare program; however,
there has not been a requirement for the use of economic evaluation to guide health care source allocation in the US public sector. The lack of US government involvement in economic evaluation has been attributed to factors such as a decentralized health care system, Americans’ distaste for rationing health care, the society’s embrace of new technology, and a political system strongly influenced by interest groups. However, economic evaluation has a strong presence among private health plans in the United States; many incorporate economic evidence in their formulary and reimbursement decisions. The lack of a neutral agency for economic evaluation in the United States can potentially make it difficult for clinicians to judge the quality of published US economic studies. Recently, the increasing financial pressure from the health care sector has formed a renewed interest for a government-funded organization to assess the effectiveness, comparative effectiveness, cost, and cost-effectiveness of health care interventions. If this initiative succeeds, economic evidence is likely to play an increased role in oncology practice in the future.

**CONCLUSION—WHY SHOULD CLINICIANS CARE ABOUT ECONOMIC ANALYSES?**

As discussed in the Introduction to this review, in addition to assessing the safety and efficacy of medical care interventions, health care budget constraints have necessitated evaluating the relative costs and benefits of these interventions. In cancer care, interventions include screening and diagnosis; medications; surgeries; radiation therapies; and a wide range of ancillary, supportive, and palliative care services. Assessing the health and economic impacts of these interventions involves a variety of issues, methods, and policy implications.

The economic impact of cancer care has received increased scrutiny due to the high cost of many newer cancer drugs, particularly biologic agents. As presented by Meropol and Schulman, the drug costs for 6 months of systemic therapy for colorectal cancer can range from less than $100 for fluorouracil/leucovorin administered daily for 5 days each month to over $50,000 for weekly treatment with cetuximab. Given this tremendous range of costs, it is crucial to consider the marginal benefits associated with more expensive agents—that is, “value for money.” Economic evaluations provide methods for assessing this value.

While this review has covered the methods used for economic analyses, we choose to conclude with perhaps the most important issue: why should clinicians care about economic analyses? To many, it seems obvious that understanding the relative costs and benefits of cancer treatment options is important. To others, only clinical outcomes and patient choices matter, and costs should never be a consideration in treatment decisions. We have identified 4 reasons as to why clinicians, in our opinion, should understand economic analyses and also consider costs as a factor in making decisions and presenting treatment options.

1. **Patient burden and decision making.** Most insurance plans require patients to pay for a proportion of the medical care services they receive, particularly for medications. With the newer biologic agents, this can mean thousands (or tens of thousands) of dollars in out-of-pocket expenses for patients, even if they have reasonable insurance coverage. For patients without insurance (or with minimal insurance coverage), personal costs may be even higher. In many cases, patients may be unable to afford the optimal treatments recommended by their clinicians. It is, therefore, important for clinicians to consider the economic impact of therapeutic choices on patients and to be able to discuss the relative costs and benefits with patients. The American Society of Clinical Oncology is planning to release guidelines to assist physicians in discussing cost issues with their patients. While economics should not be the primary driver in choosing treatments, it should certainly play a role when different treatments have similar effectiveness but vary in cost.

2. **Making assumptions, information, and decisions explicit and transparent.** Many people involved in cancer treatment, both clinicians and patients, have “internal models” regarding the costs and benefits of a particular therapy—thoughts as to whether the benefits of a treatment are worth the price.
compared with other treatment choices. Such internal models are likely to differ substantially among patients; government payers; private payers; hospitals; clinicians; and pharmaceutical, device, and biotechnology manufacturers. If these models are kept internal, it is difficult to examine assumptions about costs and outcomes and to compare these assumptions with those of patients, other clinicians, administrators, policy makers, and researchers. Only by explicitly stating what costs and benefits are being used for an economic analysis and how the analysis is being performed can there be open discussion regarding the “value for money” of a particular therapy. Further, for clinicians to be able to have discussions with their patients regarding the costs and benefits of different treatments, there must be a shared understanding of what costs and benefits assumptions are being used. Similarly, to discuss coverage decisions (and potentially appeal such decisions) with health care payers, clinicians and payers must have a shared understanding of costs and benefits. There may be disagreements regarding the costs, benefits, or methods used, but having an analysis visible to all participants will provide a useful practical point for these disagreements.

3. Prioritization. Resources are always scarce. That is, on a societal level, there will never be sufficient revenues available to fund all services desired by all members of society. This is true both for specific medical services and for broader service offerings (by government and nongovernment sources) in general. While at some level there may be a desire to provide all possible care for all patients, regardless of whether such care is associated with high costs and little chance of clinical benefit, it is necessary to prioritize expenditures to decide what is the most reasonable use of limited health care funds. However, prioritizing means establishing values for different outcomes—for example, is curing one chronic condition more or less beneficial than curing a different chronic condition? Is being able to detect 10 (or 100 or 1,000) cancers at an early stage worth more or less than being able to cure one late-stage cancer? Particularly in oncology, where many treatments are costly, economic evaluation provides an objective base for these comparisons and prioritization. It allows explicit trade-offs at the societal level, examining what must be given up (or where additional resources will need to be acquired) in order to perform a higher-priority activity. In addition, in the present system, there are clear disparities in receipt of specific treatments based on economic factors, such as health insurance status. Given the desire for a just and equitable health care system where nonclinical factors do not influence treatment choices, economic analyses can help establish which therapies are appropriate use of available resources for all individuals, regardless of their financial status.

4. High-cost therapies and the future of oncology. As discussed in item 3, there are insufficient resources to do everything that everyone wants. Given this limitation, it is important that recommended medical treatments be “good buys”—that is, reasonable uses of available resources given the value society puts on the associated outcomes (improved health and quality of life, decreased disease, postponed mortality). Economic analyses allow for demonstration of whether cancer prevention/treatment interventions are good buys compared with other medical expenditures, as well as compared with nonmedical expenditures. For oncology in particular, many recently developed therapies are associated with substantial costs. This has led to increased scrutiny of costs relative to benefits for new oncology treatments. As it is likely that many future treatments for oncology will also be very expensive, it will be even more important to justify these costs, particularly when there are limited benefits or when evidence for improved effectiveness of newer products is minimal (as may be the case for off-label treatment use).

Understanding economic evaluation and considering the relative costs and benefits of expensive new medical care interventions have been part of many areas of medicine for more than 2 decades. Economic analyses have been performed for cancer-related medical interventions for several years. However, until recently results from
economic analyses may not have affected oncol-
ogy in the same manner that these analyses have
impacted other areas of medicine; given the dev-
astating nature of cancer, society viewed almost
any expenditure to increase survival or decrease
suffering as reasonable. As advances in medicine
have resulted in cancer becoming a chronic dis-
ease in many aspects, the costs of these advances
have resulted in increased scrutiny. Further, on
a national level, recently published studies have
indicated that cost-related factors (insurance and
socioeconomic status) significantly affect diag-
nosis, treatment, and mortality among cancer
patients.66,67 Therefore, in the authors' opinions,
clinicians cannot ignore economics.
As we hope that this review has made clear,
much of economic analysis involves comparing the
costs and benefits of a medical care intervention
with one or more other interventions. Clinicians
are in a unique position to understand the health
benefits of therapies, as well as to observe the costs
(from patient, provider, health system, and poten-
tially even societal perspectives) of these thera-
pies. Insights regarding medical care costs and
benefits from members of the cancer community can be important components in discussion of the appropriate role of economic analysis in resource-allocation decisions. Perhaps this is the most compelling reason as to why members of the oncology community should be interested in economic evaluation: unless clinicians, other can-
cer health care providers, and cancer researchers
are active participants in discussions regarding the
relative costs and benefits of new interventions,
others will make these cost-effectiveness conclu-
sions. Having members of the oncology com-
pany exclude themselves from these discussions and from the process of determining costs and

benefits of new cancer therapies is unlikely to be
in the best interests of cancer patients.

SUMMARY

In summary, economic evaluation involves
the comparison of “costs” and “outcomes”
between competing interventions. The differ-
ence between the 6 types of analyses lies in how
costs are defined and outcomes are measured, as
summarized in Table 1.

Materials presented in this review should
provide readers with the concepts and knowl-
edge to understand and appraise economic eval-
uation studies in the literature. Readers who
want to learn more about economic issues in
cancer care are advised to investigate the chap-
ters by Bennett and Lee68 and Hillner and
Hayman.69 Those who are interested in con-
ducting their own economic analysis can find
excellent guidance from the classic textbooks by
Gold et al,15 Drummond et al,70 or recent books
by Neumann,71 Drummond et al (a new edi-
tion of their 1997 textbook),10 and Muenning.72
There are a variety of additional analytic issues
related to health care economic evaluations,
such as modeling disease progression beyond the
time frame of clinical trial or the estimation and
presentation of uncertainties. A technical appen-
dix is available as an online supplement to this
review to address these specific topics for read-
ers desiring additional information.

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