Cancer is the second most common cause of death in the United States, currently accounting for nearly 1 of every 4 deaths annually.¹ Not surprising, the development of innovative cancer treatments is an important focus of pharmaceutical drug development. The payoff has been meaningful, with new treatments helping to significantly increase cancer survival among men and women and in nearly all racial and ethnic groups.²,³

This improvement, however, has come at a considerable expense; the total direct medical spending on cancer care in the United States is estimated to have cost as much as $124.5 billion in 2010, with estimated expenditures of almost $160 billion by 2020.⁴ The cost of new cancer therapies has garnered the attention of a diverse constituency of patients, clinicians, healthcare payers, and public policymakers.³ As decision makers struggle for ways to better manage their budgets while providing the best care possible to patients with cancer, there is a pressing need to assess the value of cancer treatments in a rigorous and robust manner.

Of course, the question about what constitutes “value” in cancer care is a topic of ongoing discussion at all levels. Fundamentally, value is defined as the health outcomes achieved per dollar spent, but there is no universally accepted definition of what good value—or even acceptable value—means in cancer care.⁶,⁷ Value means
As innovative, high-cost cancer therapies continue to come to market, economic modeling is needed to provide better insight into the meaning of value.

Despite the refining of modeling the cost-effectiveness and budget impact of cancer therapies, serious methodologic and policy challenges remain concerning the adequacy of modeling as a sound decision-making tool in oncology.

This article is a call to action, addressing 4 key concerns related to economic modeling in oncology.

Some oncology model outcomes lack practical meaning, and model developers need to focus on informing practical decision-making.

Cost analyses should emphasize clinically meaningful rather than statistically significant outcomes.

Appropriate and robust biologic, epidemiologic, and economic data from larger trials are needed to provide meaningful parameters for oncology economic modeling.

Oncology economic models must keep pace with changing treatment paradigms, and must reflect real-world value.

Models should also address the off-label use of cancer treatments vis-à-vis personalized medicine.

As personalized medicine in oncology changes, models will need to connect economic outcomes more directly with patient outcomes.

---

As innovative new cancer therapies come to market bearing high price tags, the need for economic modeling to help provide better insight into what constitutes “value” is of paramount importance. Yet, after nearly 2 decades of cultivating and refining techniques for the modeling of cost-effectiveness and budget impact of cancer therapies—the 2 main economic models used for evaluating cancer therapies (Table 1)—serious methodologic and policy challenges have emerged that bring into question the adequacy of economic modeling, as it currently stands, as a sound decision-making tool in oncology.

As an ongoing research endeavor, in this article we are exploring some of the contentious issues in the development and use of oncology economic models as informative tools in current healthcare decision-making. Our goal is to draw attention to these complex pharmacoeconomic concerns and to promote discussion among the various stakeholders regarding the need for improvements in, and the best practices for, oncology economic modeling.

**Method**

The focus of our research is on the processes and the means by which economic models are used to evaluate healthcare technologies in oncology. We have structured our inquiry around 4 questions:

1. Are economic models adequately addressing questions relevant to oncology decision makers?
2. What are the methodologic limitations of oncology economic models?
3. What guidelines are followed for developing oncology economic models?
4. Is the evolution of oncology economic modeling keeping pace with treatment innovation?

Within the context of each of these questions, we are investigating issues related to the technical limitations of oncology modeling, the availability of adequate data for developing models, and the problems regarding how oncology modeling analyses and results are presented and interpreted. Our investigation is largely based on our years of professional experience with developing oncology economic models on behalf of the industry (ie, pharmaceutical and biotechnology corporations), insurers and other healthcare payers, and government healthcare technology assessment agencies.

Moreover, as part of our professional duties, we continuously monitor venues of published literature and activities of professional and scientific organizations to keep abreast of the latest changes and advances in pharmacoeconomics and health economic evaluation. In addition to developing numerous oncology economic models, we conduct several literature reviews annually on the economic aspects of cancer treatment, and this has afforded us the luxury of broad and deep exposure in the field of oncology economic modeling.

**Discussion**

1. **Are economic models adequately addressing questions relevant to oncology decision makers?**

Economic models typically involve the evaluation of clinical, economic, and humanistic (ie, quality of life) outcomes in 1 or more hypothetical patient cohorts defined by demographics, disease history, clinical characteristics or presentation, and other factors. Oncology-related economic models are used by pharmaceutical companies, health plans, Pharmacy & Therapeutics Committees, hospitals, clinicians, and the government (eg, Medicare, Medicaid), among many others (Table 2). Clinicians and formulary managers in oncology practice often seek a realistic understanding of the potential im-
Health Economic Modeling of Cancer Therapies

Table 1  The 2 Health Economic Models Primarily Used in the Evaluation of Cancer Therapies

<table>
<thead>
<tr>
<th>Cost-Effectiveness Models</th>
<th>Budget Impact Models</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost-Effectiveness Models</strong></td>
<td><strong>Budget Impact Models</strong></td>
</tr>
<tr>
<td>Cost-effectiveness models assess the overall clinical and economic value of a new cancer therapy in relation to existing therapies or in relation to other healthcare interventions</td>
<td>Budget impact models help to determine the financial impact of introducing a new cancer therapy within a particular healthcare setting</td>
</tr>
<tr>
<td>Estimates of clinical-economic value are generated using a variety of clinical outcomes, combined with the costs incurred by patients in achieving those outcomes</td>
<td>These models are typically used for estimating systemwide (ie, pharmacy and medical) budget impact and are frequently used by managed care payers and by other healthcare reimbursement authorities (eg, a budget impact model may be used by a hospital formulary manager to determine the impact a new cancer drug would have on the hospital’s overall budget for oncology treatments)</td>
</tr>
<tr>
<td>Many cost-effectiveness models calculate the additional cost per an additional unit gain of benefit from a therapy, with the results being presented as incremental cost-effectiveness ratios, such as cost per life-year gained or cost per clinical event avoided</td>
<td>Aside from drug costs, budget impact models typically utilize clinical data, combined with associated healthcare costs and cost offsets, all in context of the expected utilization in the healthcare system</td>
</tr>
<tr>
<td>Common approaches for constructing cost-effectiveness models may include decision tree and Markov (cohort) models</td>
<td>Results are often expressed as projections of cost per member per month</td>
</tr>
</tbody>
</table>

Health Economic Modeling of Cancer Therapies

Impacts of treatment on funding decisions about cancer therapies. Yet, given the current state of oncology economic modeling, are these healthcare decision makers receiving the proper information they need?

Our experience and observation over the years is that model developers tend to target everything and everyone possible, with the idea that analyses and results can be sorted out later by the end user (ie, healthcare decision makers). This lack of focus can lead to considerable uncertainty about what is meaningful and actionable about results and findings from modeling studies.

The issue is further compounded by the divergent perspectives of payers and providers: our experience is that the former often care mainly about direct clinical and economic outcomes (eg, cure rates, survival, costs of care), whereas the latter may care as much (or more) about other outcomes, such as the impact of treatment on patient functioning and on quality of life. Whether the current oncology economic models meet decision maker needs remains an open question, but what little has been reported in the literature suggests that, in general, economic models (not only oncology models) consistently fall short of being able to support informed decision-making.1-11

One of the reasons that oncology models may fall short of decision maker needs is that the outcomes of the models lack practical meaning. Although a variety of outcomes metrics can be generated by oncology economic models, these usually entail combinations of incremental costs and benefits of treatment to create incremental cost-effectiveness ratios (ICERs). Typical ICERs in oncology economic models are the weekly, monthly, or annual costs of survival; the quality-adjusted or progression-free survival; the cost per responder; and the cost per adverse event avoided.13,14

Based on our professional experience and what we have observed in real-world healthcare settings, there is considerable uncertainty among decision makers on what to make of these metrics—particularly the more

Table 2  Who Uses Oncology Economic Models?

<table>
<thead>
<tr>
<th>Who Uses Oncology Economic Models?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical companies (for internal decision-making)</td>
</tr>
<tr>
<td>Health economics researchers working for the healthcare industry or in academia</td>
</tr>
<tr>
<td>Health plans and integrated health networks</td>
</tr>
<tr>
<td>Physician group practices</td>
</tr>
<tr>
<td>Pharmacy &amp; Therapeutics Committees</td>
</tr>
<tr>
<td>Healthcare guideline committees</td>
</tr>
<tr>
<td>Hospitals and other healthcare institutions</td>
</tr>
<tr>
<td>Medical directors</td>
</tr>
<tr>
<td>Clinicians</td>
</tr>
<tr>
<td>Health technology assessment agencies</td>
</tr>
<tr>
<td>Government (ie, Medicare, Medicaid, Department of Veterans Affairs, Department of Defense)</td>
</tr>
</tbody>
</table>
familiar (and controversial) cost per quality-adjusted life-year (QALY). The rationale behind this metric is that it explicitly includes a common denominator that facilitates comparisons across different treatments, at various stages, and even across diseases. From a theoretical perspective, the QALY is meant to reflect benefit or utility arising from a particular treatment. In the case of a cancer therapy, improved utility may arise from improved survival or improved quality of life. From our real-world observations and professional experience, few decision makers, however, understand how the QALY is derived or how to interpret it.

The cost per QALY metric has long been an integral component of cost-effectiveness (or cost-utility) modeling of cancer therapies, and it has been regarded in some circles as the “convenient yardstick” for measuring and comparing health effects of interventions across various diseases and conditions. This metric, however, has been politically demonized in deliberation about US healthcare reform. Cancer therapies with high cost and small incremental improvement in survival or quality of life may find it difficult to meet societal thresholds for what is considered acceptable value for the money.

Therefore, the denominator of the cost per QALY metric has been a focus of debate, with the general misgivings for the QALY being well-illustrated in oncology. A patient’s health state and its associated weight may change, depending on, for example, the patient with cancer’s initial health state, or the state to which the patient’s health is raised, all of which are confounded by the rapid fluctuations in health status experienced by most patients with cancer. In addition, the practice of developing QALY weights based on valuations from members of the general population can be problematic, because such individuals may misunderstand what it is really like to have cancer.

Most people have strong emotional reactions to the idea of having cancer—cancer is dreaded more than other life-threatening conditions, such as Alzheimer’s disease, heart disease, and stroke. There are inherent difficulties collecting valid judgments on cancer health states and QALY weights by people who do not have cancer—a priori fear of cancer is not commensurate with actual experience. For these reasons, and for many others, the QALY metric shows limitations in its ability to accurately capture the value of the health gains deemed important by patients with cancer.

There is good evidence that the cost per QALY metric is not sufficiently accurate or reliable enough to be used by decision makers as a basis for the comparison of the costs of different cancer therapies. But what are the alternatives? One simple and transparent option is for costs to be related to primary health outcomes relevant to the disease in question, with emphasis on clinically meaningful findings rather than on statistically significant results.

Decisions about what defines “clinically meaningful” will require coordination between various stakeholders, including physicians providing care, managed care organizations, the government, and drug manufacturers designing and conducting clinical trials. Inroads in this area have already been made by the American Society of Clinical Oncology Cancer Research Committee. Thus, from the perspective of oncology economic modeling, greater consideration could be given to disease-specific outcomes, such as cancer progression, intensity of cancer pain, or loss of function as a result of cancer. Although Neumann and Weinstein assert that “these outcomes do not permit comparisons among diseases and conditions or between treatment and prevention,” these metrics may provide more meaningful results for clinicians and patients.

Another option is to create models that could accommodate variations in survival outcomes beyond median survival. Recent research indicates that patients place greater value on the probability—even a small probability—of a substantial improvement in survival than they do on the greater probability of smaller gain in survival. Incorporating the value of these “hopeful gambles” into models may better reflect the value to patients than current modeling strategies. This implies that there should be an increased role for behavioral economics in economic modeling of cancer therapies, at least to complement the traditional grounding of health economic models in standard economic theory.

Finally, we must also ask, is cost-effectiveness even the right metric to model? Given the life-threatening nature of cancer, neither payers nor clinicians seem particularly compelled to worry about whether a given treatment is below a threshold value for cost-effectiveness. What is likely of greater interest is the balance of comparative benefits and costs among competing treatments.

Therefore, an ideal health economic model would help decision makers assess which treatments work best for which patients under which scenarios. This question is very different from whether a given treatment meets an arbitrary threshold for cost-effectiveness.

2. What are the methodologic limitations of oncology economic models?

A variety of techniques can be used for developing health economic models, but most oncology economic models are based on decision analysis. Although oncology economic models can be enormously complex, models by definition are supposed to be simplified representations of reality. However, making generalizations and simplifications in economic models about the superiority or inferiority of one cancer therapy over another
involves accounting for vast complexities and nuances of actual clinical practice and its associated costs. Using economic models to compute overall cost-effectiveness may hide important heterogeneity, leading to the over-estimation or underestimation of particular subgroups of patients with cancer or of patients in diverse treatment settings or various healthcare systems.\textsuperscript{36-38}

All of these factors pose numerous challenges in the design and development of oncology economic models, and in the worst case can impede clear interpretation of the results generated by the models. Unfortunately, in the end, decision makers are frequently left with non-interpretable “noise.”\textsuperscript{38} Therefore, reminders are needed that these models are merely representations of reality—some representing reality quite well, with others being fictitious at best.

Oncology economic models are also inherently complex and “data hungry.” They attempt to synthesize biological, epidemiologic, and economic data from diverse sources. The availability of appropriate and robust data to populate model parameters, however, is quite limited. Traditionally, clinical trials and observational studies of healthcare interventions have provided the crucial clinical data inputs for economic modeling. Some examples include efficacy and safety data regarding disease symptoms and progression, adverse events, and death, as well as data regarding patient drug utilization behaviors (eg, therapy discontinuation or switching), all of which are used to derive probability estimates for model parameters.

Although these data may be appropriately collected, analyzed, and incorporated into an economic model, the fact still remains that they are most applicable to the intents of the original study in terms of treatment setting, patient demographics, health and disease status, and the time period over which the study was conducted. Moreover, much greater attention is paid to collecting efficacy and safety data in oncology clinical trials than to the collection of health economic data; for this reason, the quality of economic data collection may not always meet expectations or satisfy the needs of economic modeling.\textsuperscript{19}

Incentives inherent in the clinical research enterprise lead to clinical trials designed for the specific purpose of regulatory approval and maximizing market penetration.\textsuperscript{5} More often than not, economic data for oncology economic models must come from alternative sources not linked in parallel to the clinical data—such as naturalistic, noninterventional studies (including both prospective and retrospective observational studies).\textsuperscript{5} This poses problems on its own, not only from potential selection bias, but also because of the conundrum that such studies can be conducted only after the US Food and Drug Administration (FDA)’s approval of the drug label, and drug utilization and expenditure have already begun.\textsuperscript{19}

Funneling disparate clinical and economic data directly into models to examine economic questions over an extended period and across different geographic units or population subgroups is complex and fraught with opportunity for bias or outright error. This is especially true when clinical trial safety and efficacy end points are collected over short periods and explicitly omit information pertaining to resource utilization, costs, or patient preferences.\textsuperscript{40} Consequently, uncertainty about the clinical-economic benefits and harms are associated with oncology therapies, which preclude decision makers from reliably assessing the value of these therapies.\textsuperscript{5}

In many cases, clinical trial data available for use in oncology economic models are derived from small, early-phase, nonrandomized trials with only 1 study arm. According to 1 study based on data from Clinicaltrials.gov, 98% of oncology-related clinical trials registered from 2007 to 2010 have 1000 participants or fewer, and 75% have 100 or fewer participants.\textsuperscript{41} In fact, compared with cardiovascular disease and mental health clinical trials, oncology clinical trials were found to be the smallest, with a median number of 43 patients. Moreover, most (approximately 71%) of the trials were early phase (phase 0-2), and approximately 65% were single-group, nonrandomized (approximately 64%), and nonblinded (approximately 88%).\textsuperscript{41} Although these statistics reflect the reality of drug development, which appropriately designs trials for regulatory purposes, they highlight the fact that clinical trials do not reflect the experience of the majority of patients. Based on these data from Clinicaltrials.gov, small oncology trials are unlikely to be informative for establishing the effectiveness of treatments with modest effects or for comparing effective treatments to enable better decisions in practice.\textsuperscript{41}

A lack of head-to-head clinical-economic data is one of the larger problems in developing economic models for cancer therapies, especially because there tends to be more routine off-label use of cancer drugs.\textsuperscript{5} Reviews of clinical practice suggest that nearly 50% to 75% of cancer care is provided off label.\textsuperscript{5,42} Thus, data from sources other than registration-oriented clinical trials (eg, medical records and patient registries) may prove necessary to evaluate which patients do best under which treatment scenarios, and to appropriately capture the costs of treatment.\textsuperscript{5}

Although some sources of real-world data, such as comprehensive databases of healthcare claims, capture aspects of cancer-related care and its associated costs, they usually do not include the cancer disease stage and may lack other important clinical details (eg, an accurate recording of line of therapy, and positive evidence of survival). Smaller electronic medical record data sets typically capture cancer-specific data elements, but may not include non–cancer-related care and may even miss
the important aspects of resource utilization, such as cancer-related hospitalizations, altogether. Whether based on clinical trial data sets or on claims databases, even when modeling data approach the point of being adequate, it is difficult to calibrate them to the real world without real-world reference populations.44,45

Additional methodologic limitations for oncology modeling coincide with the fact that new oncology treatments are increasingly targeted at advanced (ie, metastatic) disease, and that the majority of drugs for the treatment of cancer that are coming to market have late-stage indications.12 This phenomenon results from the frequent need for an overall survival end point and the ethics of not withholding the current standard of care, which leads to trial designs that begin with patients with advanced-stage cancer who have been heavily pretreated and who have exhausted existing standard treatment options.44 Correspondingly, the majority of oncology economic models are models for late-stage disease. Therapies that may significantly improve survival and/or convey other benefits in early-stage disease often fail to differentiate themselves in late-stage, difficult-to-treat patient populations, and corresponding economic models have an intrinsic ceiling on the type and number of economic benefits that can be evaluated.44

Rarely are new economic models developed, or the old models updated, to reflect the shifts in treatment paradigms. Manufacturers struggling to justify the price of new therapies that are only applicable to a small number of patients with metastatic disease are deprived of the true real-world value, because the drugs are used in earlier lines of therapy or in larger, earlier-stage populations, where survival benefits are much greater, and the drugs are much more likely to demonstrate an acceptable effectiveness for the cost.

Conceptually, it would be interesting to compare an economic model for a cancer drug at the time of its launch, and then build variations on that model as its indications and target population expand over time (eg, 10 years later), and to compare the cost-effectiveness ratios from the before and after scenarios to observe how they change.

3. What guidelines are followed for developing oncology economic models?

In recent years, published guidelines have been made available for organizations developing and evaluating health economic models to encourage appropriate conduct for decision-making purposes. Notable examples have been published by the International Society for Pharmaecoeconomics and Outcomes Research (most recently in collaboration with the Society for Medical Decision Making),32,45,46 the Academy of Managed Care Pharmacy,47 and WellPoint.48 Most health economic modeling guidelines are a subset of comprehensive, country-specific guidelines for economic evaluation in healthcare technology assessments (eg, guidelines issued by the Canadian Agency for Drugs and Technologies in Health [CADTH] and the UK National Institute for Health and Care Excellence). Although published guidelines have provided an important foundation for standardizing economic models, they tend to be more dogmatic (ie, locked in the incontrovertible belief of their own truth) than practical, particularly for the unique challenges posed by oncology. Moreover, the speed at which economic modeling methodologies have progressed in the past 2 decades has been outpaced by advances in oncology treatment technologies. Historically, it is unclear how closely researchers have followed the guidelines for economic model development.

For oncology modeling, guideline deviation may be a consequence of accommodating the unique aspects of new treatments for cancer and the populations in which they are being applied. Without practical guidelines for developing oncology models, researchers interested in developing economic models of cancer therapies have carte blanche choice in modeling methods, resulting in inconsistent or substandard results that prove frustrating for the end users.

Although disease-specific economic modeling guidelines have been published (eg, diabetes49), only CADTH has published economic modeling guidelines that are specific to cancer, and the motivation for issuing this guidance closely resonates with the issues we discuss here.50 According to Mittmann and colleagues in a publication by the Canadian Agency for Drugs and Technologies in Health, “Current general pharmacoeconomic guidelines do not provide sufficient direction to ensure a consistent approach to the conduct of economic analyses in oncology technology assessment. The decision to develop a guidance document was based on the observed heterogeneity and quality of the analyses in oncology submissions to decision-making bodies where some of these economic analyses have been conducted in an inappropriate or misleading fashion.”50

By addressing considerations that are fundamentally important to oncology (ie, model scope, structure, and assumptions; model data choices and quality of data; as well as uncertainty, sensitivity, and validation of model results as they all uniquely pertain to cancer), the CADTH guidelines are a small but meaningful step in the right direction for improving best practices for oncology economic modeling.

It is important to note that there is no clear guidance in the United States about how or by whom the information generated by economic models should be interpreted and incorporated into decision-making processes. More-
over, because most drug formulary decision-making activities occur behind closed doors, researchers must fumble their way through the development of economic models that have a weak sense of expectations and only a vague idea about what the true goals and objectives should be. Aside from the achievement (or not) of formulary placement of a modeled cancer drug, feedback or constructive criticism of model design and presentation are rare.

4. Is the evolution of oncology economic modeling keeping pace with treatment innovation?

Oncology is one of the fastest growing therapeutic areas in the pharmaceutical industry and is also one of the most innovative, especially with new products focused on the immunologic aspects of cancer and new targets for interrupting cell proliferation. The advent of targeted cancer therapies, or personalized medicine, that allow physicians to tailor treatment to individual patients is profoundly changing the management of many types of cancer and is presenting interesting challenges in economic modeling.

What has been (or will be) the impact of cancer therapy innovation on the way health economic models are developed and perceived? For the most part, questions about the cost implications of personalized therapies are not easily answered by the hypothetical cohort simulations that are so often used in health economic models. The new heterogeneous focus in cancer treatment is creating difficulties for economic modeling, which historically evolved on the paradigm of homogeneous patient populations. Models need to incorporate not only the reality of heterogeneous populations, but also the reality of rapidly evolving treatment paradigms in which newer expensive therapies displace former standards of care that become available generically at significantly reduced costs. Models also need to address the off-label nature of treatments for cancer, but it remains unclear how to best incorporate off-label use when pharmaceutical manufacturers face regulatory restrictions that limit the promotion of the value of their products to what has been approved in product labels.

Drug reimbursement authorities and other healthcare decision makers seldom make definitive yes or no verdicts about the adoption of new therapies for cancer; rather, they tend to make nuanced judgments about how the use of medical technologies affects particular sets or subpopulations of patients. In the future, this is going to be increasingly relevant with the advent of personalized medicine that uses biomarker testing and the push toward patient-centered care, where therapies are tailored to the needs of an individual or a subpopulation, all while limiting budget exposure. We observe, however, that although we are heading in this direction, economic models continue to be developed on a one-size-fits-all basis, despite the continued reluctance of US payers to use explicit cost-effectiveness considerations to determine the value of cancer therapies.

It is likely that as personalized medicine in oncology rapidly evolves, payers will pay more attention to economic models that evaluate treatment access and healthcare resources that are directed at patients who are the most likely to benefit, and to models that tie economic outcomes more directly to patient outcomes. Although this would be a step in the right direction, genomics and other means for trying to get the right drugs to the right patients will fall flat if arbitrary or capricious thresholds of value persevere. As such, oncology economic modeling will likely be stretched from competing forces: one side pushing for generating economic evidence that will grant patients with cancer greater access to treatments, and the other side attempting to respond to fiscal pressures and the need to balance expenditures. With the drive toward obtaining system-wide efficiencies from directing resources toward patients who will gain the most benefit at the least cost, it seems clear that oncology economic models will need reorientation for predicting budgetary impact, rather than decision cost thresholds.

Conclusions

Methodologic and policy challenges in health economic modeling of cancer therapies are considerable, but perhaps not insurmountable. On one level, oncology is similar to the other areas in healthcare that are under pressure to control expenditures while maintaining or improving quality of care and patient outcomes. However, unlike many other areas in healthcare, the practice of oncology and its rapidly evolving technologies present unique challenges that make assessing and demonstrating value especially complex. There is wide latitude for improvement in oncology modeling methodologies, and the way model results are presented and interpreted. We believe that economic models are good, essential tools for helping decision makers assess complex scenarios. However, the technical and data issues associated with
oncology economic modeling raise serious questions that now require discussion within the oncology and health economics research communities. It is our hope that this article will provide a framework to guide future discourse on this important topic.

Funding Source
Funding for this study and for the preparation of this article was provided by Truven Health Analytics. An earlier, unpublished version of this study was funded by a grant from the Pharmaceutical Research and Manufacturers of America.

Author Disclosure Statement
Mr Miller and Dr Foley are employees of Truven Health Analytics; Mr Russell is currently an employee of Truven Health Analytics, and was an employee of inVentive Health Clinical and was working under contract with Truven Health Analytics at the time of the writing of this article.

References
Disruptive Innovation, Uncertain Value, and Economic Modeling in Oncology

By Michael F. Murphy, MD, PhD
Chief Medical Officer and Scientific Officer, Worldwide Clinical Trials, King of Prussia, PA

Innovations in healthcare technology frequently outpace innovations in its management. In an era of disruptive innovation, Miller and colleagues provide an insightful, richly annotated critique of health economic modeling of cancer therapeutics that is relevant to researchers, payers, and providers charged with enhancing access to therapy. Organized as a series of 4 questions, the attributes and limitations of current economic modeling for oncology products are systematically presented, acknowledging that clinical, economic, and humanistic outcomes may be differentially weighted contingent on the perspectives of diverse stakeholders. Advancing alternative strategies for data acquisition and analyses, the commentary is incisive, prompts review of the supporting literature, and creates a template for additional research and discussion.

**RESEARCHERS:** Although casting a large net during data acquisition is useful for hypothesis generation, the lack of a subsequent testable hypothesis will limit the utility of modeling as a decision-making exercise. A lack of focus may result in implications with few actionable attributes, particularly if derived data based on combinations of incremental cost and benefits are nodal points for determining access to therapy. Frequently difficult to interpret, a derived variable also may inadequately capture disease-specific outcomes for competing cancer therapies, may fail to reflect the humanistic element as a modifying variable, and may obscure the heterogeneity within the patient population treated, where much of the signal resides. Both time and geography in a disease characterized by different standards of care further limit the utility of many models, particularly if economic data are obtained through “piggybacking” on traditional registration studies, which by definition include investigators and patients who may not be fully representative of those ultimately receiving a product. Tracking patients who are ineligible for these studies in a parallel observational cohort will enhance generalizability by permitting access to naturalistic healthcare utilization data for similar patients who are not included within the original study. Nevertheless, the off-label use of oncology therapies after market authorization will require access to medical records and patient registries to complement the clinical trial data.

The concept of combining trial-based information for short-term outcomes and modeling-based economic evaluations for longer-term cost and outcomes creates an informative pathway for decision-making on a population-level development, requiring an iterative, collaborative interface between clinical trialists and economic modelers throughout the clinical development process. The alternative highlighted by Miller and colleagues, which captures temporal trends from product launch through long-term commercialization, offers a nuanced approach to a definition of “value,” acknowledging that changes in incidence or prevalence, as well as transitions in standard of care, impact the conclusions derived from basic economic modeling.

**PAYERS:** For novel therapeutic entities, it is axiomatic that the quality of data supporting economic analyses before marketing is inversely related to the level of management that is subsequently required. Within this mosaic, adoption and reimbursement technologies evaluating safety, efficacy, value for the money (cost-effectiveness), and budgetary impact represent critical domains addressed in the data set presented for review. Yet, Miller and colleagues provocatively question the propriety of an arbitrary threshold of value based on cost-effectiveness.
data across diseases, when the balance of comparative benefits and costs within competing treatments for a given cancer may be more appropriate to consider.

Limitations in traditional metrics include a lack of focus on subgroups, wherein both cost and benefit are most meaningful (targeted therapy); the time frame over which estimates are derived (temporal changes in healthcare); the geographic location and practice setting from which data have been derived; as well as the lack of formal incorporation of patient preferences and social values. Because difficult-to-treat patients with late-stage disease are frequently evaluated in the drug development process for oncology, attempts to express benefits in terms that are solely economic also will place undue influence on the traditional benchmarks that stand apart from the concerns of individual physicians and patients.

Given the limited guidelines for economic modeling specific to cancer, Miller and colleagues emphasize the importance of transparency in processes dictating coverage as a method for remediation. As in a “Gedankenexperiment,” which evaluates the likely clinical and economic viability of a proposed therapeutic before clinical development, knowledge of processes driving formulary placement and reimbursement decisions before data are actually generated and analyzed economically permits the development of more meaningful and actionable conclusions.

PATIENTS: The utility of health economic modeling to inform decision-making at the population level is well established. However, translating the results of that algorithm to the patient level can be perceived as a conflict in physician–patient relationships for providers, unless the impact of allocation of healthcare resources for other patients is also considered. Correspondingly, although an average or a median gain in benefit is arguably the least biased estimate for therapeutic utility on a population level, patients differ in attitudes regarding risk based on the dispersion of estimates of benefit versus risk surrounding these point estimates, thereby living in the standard deviations rather than at the mean.

Payers, providers, and patients therefore may view the same data and their implications through very different prisms. Economic modeling that can incorporate patient and provider perspectives using disease-specific outcomes in oncology that also resonate with the concerns of payers will better reflect the realities of decisions encountered in practice, redefining “value” in an era of innovation as much more than economics.