The Oncologist®

Value in Cancer Care

New Frameworks to Assess Value of Cancer Care: Strengths and Limitations

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Disclosures of potential conflicts of interest may be found at the end of this article.

Background

Although cancer care accounts for 5% of total U.S. health care costs, the sums being spent on treating the disease are increasing rapidly. Estimates suggest that the annual rate of spending will rise to $158 billion in 2020, from $120 billion in 2010. All sectors of the health care system contribute to this rise, including hospitals, physicians, pharmaceuticals, and new technologies, all of which are projected to be deployed to serve an enlarging number of cancer patients as the population ages [1].

Along with the many physical and emotional challenges patients must confront, a diagnosis of cancer poses enormous financial obstacles as the processes of staging, treatment, and follow-up care unfold. A national survey of cancer patients and their family members showed that among those with insurance, 25% reported that they used all or most of their savings dealing with cancer, and 33% of families reported a problem paying their cancer care bills [2]. The study also showed that among those individuals who were ever uninsured, 27% reported that they or their family member delayed or decided not to obtain care for cancer because of the cost [2]. A well-established fact is that a catastrophic illness such as cancer is an important contributor leading to personal bankruptcy [3].

Of the many domains involved with cancer care, there are cogent reasons to focus on drugs when considering how to value treatment options. Drug expenditures are rising far more rapidly than other aspects of health care and the largest expenditures by either Medicare or hospital pharmacies are for antineoplastic agents. The high costs of care, and of drugs in particular, are being passed on to patients in the form of higher premiums and high copays. The impact of this is supported by evidence suggesting that mean out-of-pocket expenses for cancer care, including premiums, can be more than $5,000/year [4]. The Kaiser Family Foundation found that worker contributions to premiums have increased by approximately 296% and deductibles have almost doubled, increasing the financial burden [5]. In one study, approximately one quarter of patients were in debt due to treatment-related expenses, and those patients reported a mean debt of $26,860 [6]. Our patients are anxious to take advantage of effective therapy whenever possible, and are also interested in discussing the cost they will bear before the initiation of treatment [7]. Despite the concern and anxiety a cancer diagnosis elicits, investigators have demonstrated that patients are sensitive to cost and have documented their willingness to tolerate higher copayments for better performing therapies. Lower predicted benefit is associated with less willingness to tolerate high copayments [8]. Surveys of practicing oncologists have demonstrated a diversity of opinion about whether to discuss costs of care, but a growing plurality is acknowledging the importance of incorporating these considerations into discussions that focus on medical management. The most recent statement of ethical principles published by the American College of Physicians acknowledges that the physician owes his or her primary responsibility to the patient, and emphasizes the importance of the physician serving as an effective steward of society's resources, in the context of caring for one's patient [9].

Frameworks to Define the Value of Cancer Care

A number of important initiatives have been undertaken to define the value of the drugs that are used to treat cancer. Each has overlapping similarities but differ with respect to purpose, focus, and means of assessment. An important consideration relevant to each of the value frameworks is the realization that value is fluid. An assessment that characterizes value at any point in time, for a specific clinical indication, may well change for the better or for the worse as different indications for a therapy are appreciated and as unexpected toxicities emerge. An agent that has modest efficacy in the advanced disease setting may favorably impact long-term disease-free survival when used in an adjuvant setting. The discussion that follows will describe each framework in greater detail. Table 1 demonstrates a number of properties of each of these.

The American Society of Clinical Oncology Value Framework

Stimulated by the projected rises in costs of cancer care and their impact on our patients, the American Society of Clinical

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Table 1. Differing frameworks assessing the value of drugs

	Primary purpose	Treatment modalities assessed	Data source informing framework	Scoring/grading	Cost	Updating
ASCO [10]	Shared decision-making, patients/ MDs	Pharmaceuticals for solid tumors, hematologic malignancies	Clinical trial	Net Health Benefit Score (NHB)	Cost/month (advanced disease), cost/ course (adjuvant disease)	Dynamic-value changes as impact of agents change
ESMO [11]	Inform public policy, clinical guidelines, day-to-day clinical situations	Pharmaceuticals for solid tumors	Clinical trial	(A,B,C) for adjuvant disease; (5, 4, 3, 2, 1) for advanced disease	N/A	Not stated
NCCN [12]	Providers and patients, as well as other stakeholders involved in the treatment decision-making process	Systemic therapies in all major cancer types, radiation oncology, imaging, surgical interventions	Clinical trials and expert consensus	Evidence Block Score (5, 4, 3, 2, 1)	Affordability scale (1–5)	Annually updated, changes as impact of therapies change
ICER [13]	Inform society; inform policymakers/payers	Drugs, devices, procedures, and delivery system innovations	Clinical trials, econometrics	Evidence rating matrix	Care value (expressed as a QALY) and health system value (judging long-term value)	Reports for individual areas commissioned, updating uncertain
Drug Abacus [16]	Inform policymakers and physicians	FDA-approved drugs since 2001	Public data the company sent in to the FDA to obtain approval	Abacus price varies with clinical benefit, toxicity, innovativeness, etc.	Abacus derived "price" based on above variables vs. industry-specified price	Enhancements planned but not explicitly stated

Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; FDA, U.S. Food and Drug Administration; ICER, Institute for Clinical and Economic Review; N/A, not addressed; NCCN, National Comprehensive Cancer Network; QALY, quality-adjusted life-years.

Oncology (ASCO) Task Force on Value in Cancer Care was charged with developing a framework with which to assess the relative value of treatments available to the oncology patient. The focus of this initiative was on medical therapies because these are the modalities most relevant to the practice of medical oncology. The wide array of treatment options, their attendant clinical impact, and cost to the patient suggested the importance of developing a framework with which to assess new therapies. The urgency to do so is emphasized by the fact that the top 10 drugs that Medicare reimbursed under Part B are drugs used for cancer treatments. Furthermore, many antineoplastic agents that are approved for use by the U.S. Food and Drug Administration (FDA) offer modest improvements in progression-free or overall survival when compared with a prevailing, less costly standard of care.

The fundamental purpose for developing the value framework is that it will serve as a tool in the process of shared decision-making between physician and patient. To this extent, it is important that physicians are fully informed about the clinical effects and toxicities of a regimen to be considered for a patient, as well as the underlying costs associated with the antineoplastic agent and the required supportive medications. The initial ASCO value framework was published in July 2015 [10]. The framework is based on data derived from a prospective randomized trial in which a comparator was tested against a standard of care. An exception to this is in the setting of antineoplastics that have been approved on the basis of promising activity seen in a single-arm, noncomparative trial, in which case there is not a comparator. Two frameworks have been developed: one for advanced disease and the other for potentially curative disease (adjuvant therapy). Each addresses three essential domains in the assessment of an agent's value: clinical benefit, toxicity, and cost. The advanced disease framework is designed to have the relative weights (importance) be modifiable according to patient preference. Specifically, if the patient's highest priority is freedom from symptoms, the toxicity score can be more heavily weighted than survival. Bonus points are awarded for especially desirable outcomes such as symptom palliation, improvement in quality of life, and significant improvement in survival at the tail of the curve. If, in the advanced disease setting, the patient's most important goal is length of life over freedom from symptoms, the weighting for overall survival (OS) and progression-free survival (PFS) can be increased. The vision is for the development of a personalized tool that can be used to assist patients in deciding what therapy is best for them based on their wishes.

The composite of the clinical benefit, bonus points, and toxicity scores is tallied to generate a net health benefit. It is meant to be a measure of the relative improvement a new regimen has yielded when compared with the control therapy against which it was compared in the clinical trial.

The direct costs of the antineoplastic agents and the requisite supportive care medications constitute the costs that the framework displays. Indirect costs, such as unplanned emergency department or hospital visits and time lost from employment, are not included. The costs shown are both the costs of purchasing the medications in the regimens compared

in the relevant trial and the patient's copay for the regimen, based on their particular insurance policy. Neither quality-adjusted life-years nor incremental cost-effectiveness ratio are included in this analysis, because the focus is the physician-patient decision-making process.

In clinical practice, there might be several regimens that are appropriate for a specific clinical indication. It is envisioned that the patient will be shown the value assessment for each of these. Each can be displayed with respect to the clinical benefit expressed through survival advantage (e.g., time gained), symptom relief, impact on quality of life, side effects to be anticipated, and the costs of the treatment regimen, as well as the mandated copayment when compared with the comparator against which they were compared in the clinical trial.

To be effective as a tool for shared decision-making, use of the framework must fit into the workflow of a busy clinical practice. A software-driven tool is envisioned that will be prepopulated with the relevant trial data on which value assessments can be made, and produce on-demand options to be considered for the clinical scenario facing the patient. Were the ASCO framework to evolve for use as a policy-making tool, a more conventional characterization of comparative effectiveness would be appropriate.

The European Society for Medical Oncology Magnitude of Clinical Benefit Scale

The European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (ESMO-MCBS) [11] represents an ambitious initiative by European oncologists and biostatisticians to define a set of metrics that support the clinical benefit of antineoplastic agents in a particular clinical setting. The basis for this undertaking is the rising costs of cancer care, and of pharmaceuticals in particular; the varying availability of useful cancer medicines; and uneven outcomes in treating cancer throughout Europe [14].

The fundamental principles underlying the ESMO framework are that overall survival or, in appropriate instances, cure, take primacy over surrogates such as progression-free survival or response rate. Direct endpoints such as disease-free survival (DFS) in curative disease are regarded as a more valid surrogate in curative scenarios (adjuvant or neo-adjuvant therapy) than PFS is in the setting of incurable disease. Scores are awarded by virtue of improvements in the variables under investigation in a comparative trial or cohort study. The highest ratings are awarded for prespecified endpoints of OS and DFS, whereas lower ratings are awarded for PFS, time to progression, or quality of life in the noncurative setting. Clinical benefit in either the advanced or potentially curative settings is judged by both the hazard ratios achieved and absolute improvement in the prespecified clinical endpoint defined for the trial in question. For the curative setting, the scores awarded are based upon achieving threshold levels of hazard ratios (HRs) and absolute time difference compared with the control, and the test regimens are awarded grades of either A, B, or C. A and B grades are regarded as sufficiently clinically meaningful to justify consideration by a health technology assessment agency for inclusion in a nation's compendium of approved drugs or regimens. In the advanced disease setting, the scores are graded on a scale of 1 to 5 (5 is highest). Higher ratings are awarded for clinically meaningful improvements in the most important endpoints (e.g., OS), and lower ratings for a less well-validated surrogate such as PFS. The scores can be favorably or unfavorably affected by toxicity or significant changes in quality of life. In the advanced disease setting, clinically meaningful outcomes are those achieving a point score of 4 or 5, and it is these that are deemed suitable for further analysis through cost-effectiveness assessments [11]. For the adjuvant setting, the magnitude of difference in HR and median OS or DFS is weighed against toxicity and impact on quality of life, if measured. The highest scores are categorized as A and B.

A particular strength of the ESMO-MCBS is the breadth of expertise aggregated to the task force that developed the evaluation system, which included medical oncologists and biostatisticians. ESMO's MCBS scoring finds a relative degree of concurrence with the work on clinically meaningful outcomes undertaken by the ASCO Cancer Research Committee that recommended thresholds for OS, PFS, and HR for first-line therapy for advanced lung cancer, pancreatic, colorectal, and triple-negative breast cancers [15].

The ESMO-MCBS does not address the issue from the perspective of communication between physician and patient (although this is not implausible should a patient inquire) who are discussing a management plan; rather, it is designed as a formal advisory tool to ministries' policymakers. Moreover, cost is absent from this framework because the European nations have their own economic considerations and unique drug-pricing outcomes. Rather than grapple with this complexity, the ESMO-MCBS has determined to leave out considerations of cost when evaluating the value of oncology drugs. Whether this situation is one in which the MCBS will be used is uncertain. Thus, it is a policy tool, not a tool to be deployed at the clinical interface.

National Comprehensive Cancer Network Evidence Blocks

The National Comprehensive Cancer Network (NCCN) has incorporated evidence blocks into the guidelines it has promulgated for a wide variety of clinical scenarios [12]. These are designed to provide physician and patient with a graded assessment of the important variables that go into implementing a particular treatment regimen based upon NCCN guidelines. The domains include effectiveness, safety, quality of evidence, consistency of evidence, and affordability. These are similar to those already mentioned in the ASCO and ESMO value frameworks, and the Institute for Clinical and Economic Review (ICER) framework that is discussed in the next section. Each domain is graded 1 (least favorable) through 5 (most favorable).

While seemingly simple to use, the available information suggests that the scoring is subjective, because the evidence blocks lack specificity for defining each level of scoring. However, a panel of experts in each cancer area constitutes the guideline committee for a specific cancer type. Thus, one can assume the final score for any domain represents a preponderance of opinions of the convened expert panel. The affordability domain includes drug cost (to whom is uncertain), supportive care, administration costs, and monitoring and management of toxicity. It is not clear how each of these costs is determined and thresholds for a regimen categorized as very

expensive (score of 1), or very inexpensive (score of 5) are not defined. Of the first 10 tumor types to have evidence blocks published, only 24 drugs (out of 501 ratings) have been rated a score of 1 on affordability, with none receiving a rating score of 5.

Institute for Clinical and Economic Review

ICER is an independent, nonprofit, research-based organization that produces independent reviews of the comparative clinical effectiveness and value of medical tests, treatments, and delivery-system innovations. The stated goal of these reviews is to catalyze and support collaborative efforts among stakeholders to disseminate and implement evidence-based best practices—through patient and provider tools, payer policies, and policymaker initiatives—to improve the quality and value of health care services. In 2016, ICER will produce its first drug reviews for oncology agents, including those in lung cancer and multiple myeloma.

The assessments are based on two primary evaluations: care value and health-systems value [13]. Care value is a judgment of the average per-patient costs, clinical outcomes, and broader health effects of two alternative interventions or approaches to care. Health-systems value is a judgment of the degree to which the short-term budget impact of a new care option can be afforded by the health care system. These elements reflect a broader level of analysis, taking a holistic approach to drug review and assessment.

Care value is arrived at by panel discussion and evaluation of four key elements: comparative clinical effectiveness, incremental cost per clinical outcome, contextual considerations, and other benefits or advantages that might not be reflected in the clinical review or profile. The factors accounted for in this review overlap with many of the elements included by ASCO and the other organizations. The process with ICER is much more iterative, including assimilation of various elements and meta-analysis of all evidence, providing one review of the product in a particular clinical context.

Economic components are further evaluated in the health-system value phase of assessment by modeling care-value price into the expected budget impact in the United States. This evaluates the total costs to society, reflecting, again, a very different viewpoint from the other value frameworks. How this will fulfill its mission to aid multiple stakeholders is yet to be determined, but it adds to the environment where value is at the forefront of decision-making in providing care to the patient with cancer.

Memorial Sloan Kettering Cancer Center Drug Abacus

The Drug Abacus is the creation of a physician and policy expert at Memorial Sloan Kettering Cancer Center in New York. This tool contains a convenience sample covering 54 cancer drugs approved between 2001 and 2015 by the FDA for the treatment of cancer. In contrast to the other value frameworks, the output of the Drug Abacus is not a value score, per se, but rather an "Abacus Price" that represents the theoretical price the agent should be, according to the user. This theoretical price is juxtaposed onto the actual market price to contrast any price deficits or surplus for a given antineoplastic agent [16].

The Abacus price is calculated using a formula that consists of weightings of factors used in other frameworks. Elements such as efficacy, toxicity, or population health burden are common to other value frameworks. However, the Drug Abacus also includes other factors such as research and development, rarity, and novelty, which are not commonly included in other assessment tools. The utility of these elements to individual patients or physicians may relate less to the day-to-day treatment decision process but may be more relevant for policymakers or from a societal perspective. Similar to the ICER assessments, a broader societal view often detaches the assessment tool from the immediate treatment decision, by inclusion of these other elements. Finally, the source of the clinical data in the Drug Abacus comes from the FDA package insert and, thus, is reliant upon data that make it into product labeling at the time of launch, however much or little this may be.

Summary and Future Prospects

The astonishing rate at which new therapies are being introduced into the oncology compendia is a reflection of the massive expansion in our understanding of cancer biology and its translation to the clinical interface. These awe-inspiring advances have, on occasion, been translated into therapies with profound impact. In many instances, particularly in the advanced-disease setting, they have led to new agents that result in incremental improvements. For every "game changer" there are many drugs that provide more modest impact. None of this is to refute the possibility that agents resulting in modest improvement in metastatic disease might add to an existing regimen and yield a marked positive impact in the adjuvant setting. Value is a dynamic concept; a new agent might be assessed a low value rating when initially tested in metastatic disease but achieve a high rating in the adjuvant setting. An example is trastuzumab, which had a positive impact on the therapy of HER2-amplified metastatic breast cancer but was not curative [17, 18]. When this agent was combined with chemotherapy in the adjuvant setting, substantial improvement in long-term disease-free survival was observed when compared with chemotherapy alone [18]. The value to the patient and to the health care system is very different in these two scenarios.

Confronted by the reality of new agents or regimens having different clinical impacts in different clinical situations, the rising cost of cancer care, and the financial burden that high drug prices entail for many insured and underinsured patients, a number of influential professional organizations have developed models with which to assess the clinical benefit and value of cancer treatment regimens. The goal is to develop a system of valuing medical therapies that is characterized by alignment between the benefits and costs (in terms of physical and financial toxicity) of the therapy to our patients.

The ESMO-MCBS and the ASCO model frameworks are the most explicit in characterizing and quantifying degrees of clinical benefit, toxicity, and impact on quality of life. The NCCN evidence blocks cover the same domains in determining efficacy and safety, although the criteria used to achieve a score is less well defined than the other two. ICER takes a somewhat different tack in that the analysis takes into account comparative clinical effectiveness of an agent across many

trials, and provides an economic analysis of the impact of an agent on the health care system.

These tools have varying purposes. The ESMO initiative is designed to provide data on the relative clinical impact of agents for a given disease scenario and to leave comparative effectiveness calculations to the various European health technology assessment committees. The ASCO tool has been developed to assess net health benefit and demonstrate cost of the agent(s) as these are discussed in the process of shared decision-making by oncologist and patient. No attempt has been made to undertake formal cost-effectiveness analyses, as in the ICER approach, because this effort is largely focused on the doctor-patient conversation. The NCCN initiative is also designed as a tool with which to discuss the variety of regimens that can be offered to a patient, supplemented by an assessment of affordability.

Harmonizing approaches such as these is likely to bring a consensus to bear on how we value agents to treat cancer. These initiatives are at the vanguard of a debate on the obvious demand of the consumer to "get what you pay for" and of society to reduce health care costs. It is plausible that raising the question of fair pricing could lead to a downward trend in willingness to pay for drugs that have only modest impact. In parallel, we must answer how to encourage innovation that benefits patients and the system in the long run.

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References

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

2. USA Today, Kaiser Family Foundation, Harvard School of Public Health: National survey of households affected by cancer. Available at http://www.kff.org/ kaiserpolls/7590.cfm. Accessed May 18, 2016.

3. Himmelstein DU, Thorne D, Warren E, Woolhandler S. Medical bankruptcy in the United States, 2007: Results of a national study. Am J Med 2009;122:741–746.

4. Bernard DSM, Farr SL, Fang Z. National estimates of out-of-pocket health care expenditure burdens among nonelderly adults with cancer: 2001 to 2008. J Clin Oncol 2011;29:2821–2826.

5. Henry J. Kaiser Family Foundation. 2015 Employer health benefits survey. Available at http://kff.org/ report-section/ehbs-2015-summary-of-findings/. Accessed May 18, 2016.

6. Shankaran V, Jolly S, Blough D et al. Risk factors for financial hardship in patients receiving adjuvant chemotherapy for colon cancer: A population-based exploratory analysis. J Clin Oncol 2012;30:1608–1614.

7. Bullock AJ, Hofstatter EW, Yushak ML et al. Understanding patients' attitudes toward communication about the cost of cancer care. J Oncol Pract 2012;8: e50–e58.

8. Wong YN, Hamilton O, Egleston B et al. Understanding how out-of-pocket expenses, treatment value, and patient characteristics influence treatment choices. ***The Oncologist*** 2010;15: 566–576.

9. Snyder LS. Review of the American College of Physicians Ethics Manual: Sixth edition. Ann Intern Med 2012;156:73–104.

10. Schnipper LE, Davidson NE, Wollins DS et al. American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 2015;33:2563–2577.

11. Cherny NI, Sullivan R, Dafni U et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2015;26: 1547–1573.

12. National Comprehensive Cancer Network. Available at http://www.nccn.org/evidenceblocks/pdf. Accessed May 20, 2016.

13. Institute for Clinical and Economic Review. Methods. The ICER approach. Available at http://icer-review.org/methodology/icers-methods/. Accessed May 20, 2016.

14. De Angelis R, Sant M, Coleman MP et al. Cancer survival in Europe 1999-2007 by country and age: Results of EUROCARE–5-a population-based study. Lancet Oncol 2014;15:23–34.

15. Ellis LM, Bernstein DS, Voest EE et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014;32:1277–1280.

16. Memorial Sloan Kettering Cancer Center. Drug Abacus. Available at http://www.drugabacus.org/ drug-abacus-tool. Accessed May 20, 2016.

17. Seidman AD, Fornier MN, Esteva FJ et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. J Clin Oncol 2001;19:2587–2595.

18. Perez EA, Romond EH, Suman VJ et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: Planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol 2014;32: 3744–3752.

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