The Importance of Economic Perspective and Quantitative Approaches in Oncology Value Frameworks of Drug Selection and Shared Decision Making

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SUMMARY
The debate around value in oncology drug selection has been prominent in recent years, and several professional bodies have furthered this debate by advocating for so-called value frameworks. Herein, we provide a viewpoint on these value frameworks, emphasizing the need to consider 4 key aspects: (1) the economic underpinnings of value; (2) the importance of the perspective adopted in the valuation; (3) the importance of the difference between absolute and relative measures of risk and measuring patient preferences; and (4) the recognition of multiple quality-of-life (QoL) domains, and the aggregation and valuation of those domains, through utilities within a multicriteria decision analysis, may allow prioritization of QoL above the tallying of safety events, particularly in a value framework focusing on the individual patient.

While several frameworks exist, they incorporate different attributes and—importantly—assess value from alternative perspectives, including those of patients, regulators, payers, and society. The various perspectives necessarily lead to potentially different, if not sometimes divergent, conclusions about the valuation. We show that the perspective of the valuation affects the framing of the risk/benefit question and the methodology to measure the individual patient choice, or preference, as opposed to the collective, or population, choice.

We focus specifically on the American Society of Clinical Oncology (ASCO) Value Framework. We argue that its laudable intent to assist in shared clinician-patient decision making can be augmented by more formally adopting methodology underpinned by micro- and health economic concepts, while recognizing that behavioral economics may provide additional thinking: (1) reintroduce the debate around the concept of value in more formalized microeconomic terms; (2) clarify the importance of the economic perspective adopted in the valuation; (3) critically appraise the use of certain statistical measures in the context of the patient-HCP interaction, specifically the difference between relative and absolute measures of risk, as well as using formal patient-preference methodology; and (4) provide rationale supporting the foregoing of safety parameters for higher-order utilities.

Definitions of Value
The term “value” in health care is used abundantly, yet a single definition does not appear to exist nor is likely to emerge. The main reason for this lack of definition can be found in a phrase from economist Joan Robinson about the related concept of utility. She writes: “Utility is a metaphysical concept of impregnable circularity; utility is the quality in commodities that makes individuals want to buy them, and the fact that individuals want to buy commodities shows that they have utility.” Ultimately, the value of a commodity depends on one’s willingness to trade for something else that has value. This may be the remote risk of a serious side effect for the possibility of additional years of life or anything else that has value.
Thus, when following this idea, one might question whether it is correct to define value, as suggested by Porter (2010), to contain a numerator and a denominator, with outcome being the numerator and costs being the denominator:

1. Value = Outcome ÷ Cost

Nevertheless, in the U.S. third-party payer context, Equation 1 may be viewed as a generally accepted way of expressing value. Equation 1 may also be viewed as a cost-consequence analysis, in which outcomes and costs are tallied, yet not aggregated, into a single measure. Equation 1 expresses the ratio of an intervention’s outputs for its cost; for example, the intervention produces, on average, 21 months of survival for a given cost of, say, $100,000. Therefore, the value according to Equation 1 is \( 1.75 \) (life-years) ÷ $100,000, or expressed in words: “Providing 1.75 years of life for a cost of $100,000.”

For the advanced disease setting, the outcome measures in the updated version of the ASCO Value Framework include the hazard ratio (HR) for overall survival (OS) or progression-free survival (PFS), median OS or PFS or response rate (RR), toxicity, an assessment of the tail of the survival curve, palliation, QoL, and the absence or presence of a treatment-free interval. For the adjuvant setting, the outcome measures include the HR for OS or disease-free survival (DFS), median OS or DFS, toxicity, and the tail of the curve. The ASCO Value Framework may be viewed as a cost-consequence analysis in which an actual score for the consequences is tallied up and juxtaposed against the wholesale acquisition cost and/or the patient copay. Hence, the ASCO framework is a major step forward from Equation 1, since it aims to quantify good value.

Another measure, introduced over 40 years ago and used in formal economic evaluation, or cost-effectiveness analysis (CEA) of health care interventions, is called the incremental cost-effectiveness ratio (ICER). This measure is a key criterion of the value framework of the Institute for Clinical and Economic Review. It becomes apparent that, while some of the questions addressed in the various value frameworks and include the types of questions that these different stakeholders may ask. Table 1 illustrates the need to be precise about how the attributes addressing these questions would have to be communicated. It becomes apparent that, while some of the questions that different stakeholders might ask require the same measures of benefit (i.e., risk reduction), many questions invoke the need for different concepts.

In the next section of this article, we focus on the individual patient’s perspective, as opposed to the population viewpoint that regulators and payers need to take. Table 1 highlights that, unlike other stakeholders, individual patients as consumers of health care are more likely to ask questions in terms of chance and generally ask questions in absolute terms, such as: “How long (requires an absolute measure) may I expect (invokes probability) to live with this condition?” This type of questioning has important implications for the measures of benefit that can be used to answer such questions, while also considering probability-based answers.

To illustrate the individual patient perspective further, we outline potential relevant risk reduction measures and paraphrase the ways these measures would have to be articulated in an HCP-patient interaction. Table 1 attempts to explain the
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Measure of benefit in readily understood terms, while holding true, as much as possible, to their formal statistical definitions. Finally, oncology can also take a page from extensive risk prediction work in the cardiovascular space, with equations such as the Framingham risk equations, where simple online risk calculators allow one to estimate a patient’s absolute 10-year risk of death based on a set of validated risk factors or covariates.46

Measures of Risk and Their Relevance to the Individual Patient

In Table 2, we use definitions of various measures of relative and absolute risk as they would need to be explained to a patient in an HCP-patient interaction. Table 2 helps clarify why absolute measures of risk are generally better ways to assist a patient, as a health care consumer, in shared decision making.

| TABLE 1 | Perspectives of Stakeholders Relevant to Value Frameworks in Immuno-Oncology |
| --- | --- | --- |
| **Stakeholder** | **Perspective** | **Wants to Understand** |
| Patient | Consumer of health care intervention | What happens if I take the drug? What happens if I don’t? Invokes probability and independent predictors of survival (if known) |
| | | What are my chances of the drug working? Invokes probability and risk factors |
| | | How (much) long(er) will I live? Invokes probability, mean survival, median survival, and the shape of the survival curve |
| | | What is my chance of living another year? Invokes the shape of the survival curve and potentially certain trade-off decisions |
| | | What is my chance to be a “long-term” survivor? |
| | | Will I be able to function and do the things I used to? Invokes quality measures of survival and their measurement and uncertainty |
| | | Will I be able to continue on “as normal,” or not? |
| | | Is this drug safe for me to take? Invokes probability and absolute rates (% of AEs, SAEs, NNH |
| | | How much will this cost? Invokes cost measures, such as copay amounts, deductibles, and potentially lifetime caps |
| Health care provider | Provider of health care intervention | Do I have a reasonable expectation that the intervention will work in my patient? May be a mix of relative and absolute measures of effect. Invokes probabilities and (if data exists) potential (patient-individualized) risk-stratification |
| | | How can I minimize/avoid causing harm? Absolute rates (% of AEs, SAEs and an assessment of the “risk/benefit” profile |
| | | How can I improve the overall well-being of the patient? Invokes QoL considerations and psychosocial domains |
| Regulator | Assessor of “risk/benefit ratio” (safety and efficacy) | Is the clinical effect proven and do the efficacy outcomes outweigh the adverse effect profile? Specifically: |
| | | (a) Did the study meet its primary endpoint, secondary endpoints (if a hierarchical test was employed)? Key measure of effect is the HR Additional measure is (incremental) median survival Other measures can relate to (statistics of) secondary endpoint(s) |
| | | (b) Do we believe the drug’s adverse effect profile to be acceptable, given the remaining level of medical unmet need in this disease state? Absolute rates (% of AEs, SAEs and an assessment of the “risk/benefit” profile |
| Payer | Health care system | Similar questions as the regulator AND |
| | | Does the trial population address the population I am covering? Requires RWD and potentially additional modeling approaches |
| | | How many patients need treatment to avoid 1 event? Invokes ARR and NNT (1/ARR) |
| | | Is the comparator drug relevant? Relates to the standard of care and “next best alternative” for marginal analysis in health economics |
| | | What cost offsets did the drug show, if any? Requires a cost-consequence analysis |
| | | What is the price? Requires financial modeling |
| | | What is the anticipated volume of patients and what is the impact on my budget? |
| | | Does it provide value-for-money? Requires Equation 1 or 2 |
| | | Is it cost-effective? Requires Equation 2 |
| Society | Society as a whole | Is there ancillary value to society outside of “direct medical costs,” by way of “indirect costs,” such as reduced absenteeism, presenteeism, and avoiding loss of work productivity? Requires indirect costing methodology, time and motion studies, and patient-preference methodology |

Note: Mean survival can be readily shown to be equivalent to the area under the survival curve; hence, incremental mean survival can be shown to be equivalent to additional months/years of life gained.52

AE = adverse event; ARR = absolute risk reduction; HR = hazard ratio; NNH = number needed to harm; NNT = number needed to treat; QoL = quality of life; RWD = real-world data; SAE = serious adverse event.
decision making, compared with relative measures, since they more directly provide answers to questions of most interest to patients.\(^4\) It is also noted that the standard, relative measures of risk used in regulatory evaluations, in particular, fall short in addressing the types of questions that patients likely have regarding a therapeutic immuno-oncologic intervention. The regulatory perspective is included in Table 1 to underscore the context for relative measures of risk required for regulatory evaluation, which often shape the HCP perspective and vernacular of communicating risk, as reflected by the ASCO Value Framework. In addition, Table 2 clarifies that probability and preference-based concepts can further facilitate capture of the individual patient perspective.\(^5\)

The exercise of articulating the measures used in the value frameworks, with the patient as the audience, clarifies the following: Relative measures of risk reduction, such as relative risks, odds ratios, and hazard ratios (HR), are difficult to articulate correctly and intuitively to a layperson. In

### Table 1: Select Measures of Risk and Their Articulation in a Putative HCP-Patient Interaction

<table>
<thead>
<tr>
<th>Stakeholder/Perspective</th>
<th>Wants to Understand</th>
<th>What Measure of Risk Reduction Can Address the Question?</th>
<th>Measure in Value Framework(^a)</th>
<th>How Might the Answer be Articulated Within the HCP-Patient Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient/consumer of health care intervention</td>
<td>How (much) longer will I live?</td>
<td>Using incremental median survival</td>
<td>ASCO, ESMO</td>
<td>“Fifty percent of the population studied in the trial of this drug survived for 16 months. This was 4 months longer than for the drug with which it was compared.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Using the HR</td>
<td>ASCO, ESMO</td>
<td>Strict definition: The treatment in question will cause the patient to reach death more slowly (delay death) compared with the alternative; a treated patient that has not yet died by a certain time has a chance of dying at the next (measured) time point, defined by the HR (i.e., if HR = 0.5 then chance = 50%).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Using incremental mean survival = life-years gained</td>
<td>MSKCC</td>
<td>“The average patient in the trial survived for 19 months. This was 4 months longer than for the drug with which it was compared.”</td>
</tr>
<tr>
<td>What is my individual chance of being one of those long-term survivors?</td>
<td>Using probability of survival</td>
<td>Not captured explicitly in any framework. ASCO mentions “landmark” (%) survival at survival times relevant to the tail of an immuno-oncology survival curve</td>
<td>ASCO, ESMO</td>
<td>“There appear to be about 20% of patients that survive beyond 3 years.”(^c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Using the shape of an immuno-oncology survival curve (as opposed to that of chemotherapy)(^d)</td>
<td>ASCO updated framework has bonus points for the tail; none include patient preference</td>
<td>“Using this immuno-oncology agent, there are/apppear to be some patients who survive (more) long-term… the science to predict your individual chance needs to evolve to be able to answer your question for you specifically.”(^c,d)</td>
</tr>
<tr>
<td>Will I be able to continue on “as normal,” or not?</td>
<td>A measure that can be used is the Trial Outcome Index, which assesses QoL and functional well-being</td>
<td>QoL is acknowledged in ASCO, ESMO, and ICER value frameworks</td>
<td>“There were some meaningful improvements observed in QoL and functional well-being of the patients that were studied.”</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)The NCCN Evidence Blocks are not mentioned in this table, since they do not at this time explicitly provide clarification of which measures to use to estimate value, unlike the ASCO, ESMO, MSKCC, and ICER frameworks.

\(^b\)This definition is often reported in the medical literature.\(^9\)

\(^c\)For simplicity, we assume that there are no known risk factors for the condition or indications to predict long-term survivors.

\(^d\)The NCCN Evidence Blocks are not mentioned in this table, since they do not at this time explicitly provide clarification of which measures to use to estimate value, unlike the ASCO, ESMO, MSKCC, and ICER frameworks.
addition, literature supports the use of absolute measures of risk in oncology patient communication, since unlike relative risks, they do not tend to overestimate the magnitude of the benefit as perceived by the patient.31,43-45

In addition, such measures, while particularly valuable from a regulator’s perspective, are much less so from an individual patient perspective. Absolute measures of risk reduction, such as additional months of survival, are more intuitive to the patient and therefore can be considered more “patient-relevant.” The revision of the ASCO Value Framework also acknowledges some of these issues: “To avoid the misinterpretation that a favorable HR necessarily represents a large absolute gain in OS or PFS, it is incumbent upon the physician, at the point of care, to explain the absolute difference in survival (e.g., on average, a patient can expect an improvement of x weeks or months) with the test regimen when compared with the standard of care. It is essential to understand that the framework is meant to be modified at the point of care, as a physician and patient finalize a regimen.”31 The ESMO Value Framework has recognized this also and reports on the relationship between the HR and incremental months of OS, scrutinizing for face validity, coherence, and consistency.7

It is important to note that with an individual patient in mind, the individual’s likelihood of an event also needs to be considered. Even a concept such as mean, or average, survival,31 while arguably more accurate from a patient’s standpoint than median survival, does not account for the individual patient perspective. Note that use of the word “average” in the ASCO Value Framework is incorrect. “Average” equates to the restricted mean survival, which is mathematically equivalent to the area under the curve in the absence of censoring. Mean survival is by definition greater than median survival for survival-time distributions, which are typically right-skewed; this point is particularly relevant for immuno-oncology survival curves demonstrating the now well-known tail (i.e., displaying nonproportional hazards behavior).46-48

However, mean survival also does not allow for the patient’s preference to be accounted for in a meaningful way. For instance, it has been shown that a majority of cancer patients prefer a “hopeful gamble” (i.e., providing a lower possibility of longer-term survival, such as might be afforded by the tail of an immuno-oncologic) over a “safe bet” offering a certain median survival and thus may be willing to accept a risk of greater short-term mortality in exchange for a lower chance at a large, more meaningful gain in survival.47 The updated ASCO Value Framework does recognize the value of the tail in immuno-oncology and has incorporated this into its updated framework,31 but it does not yet go as far as considering patient preference related to the possibility of being part of that tail.

Multicriteria Decision Analysis, QoL, and Utility

One might argue that all value frameworks may be viewed as simple, practical forms of multicriteria (attribute) decision (utility) analysis. Utility is a way of valuing QoL and represents an individual’s relative satisfaction with a health state, on a scale from 0 (representing death) to 1 (representing perfect health).42 The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is an instrument frequently used to measure quality of life in cancer patients.48 The EQ-5D is a well-described utility instrument aimed at valuing general health through domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.46-48 Efforts to map the relationship between the EORTC QLQ-C30 and EQ-5D-based utility values at the individual patient level have been performed.48 This field continues to evolve and is worth tracking closely to gain further insight into how individual patients value various QoL domains.

These QoL considerations may supersede individual side effects, since their implications tend to “ladder up” to more overarching QoL considerations. This therefore raises the question of whether in a value framework intended for the individual patient, the safety of a compound can be left out altogether as long as an acceptable form of capture of patient-relevant QoL is included and valued in a utility score.50

Discussion

The concept of value in oncology has gained tremendous traction over the last few years. While there exist various definitions of value, some qualitative (e.g., Equation 1) and some quantitative (e.g., Equation 2), perhaps the most important aspect in this debate is to be thoughtful about what definition of value may be most appropriate, given the perspective of the audience (see Table 1). We have focused on the ASCO Value Framework and its laudable intent to attempt to clarify elements of value that can be communicated within the HCP-patient interaction. We performed a mental exercise of articulating various measures of risk and critically appraised their relevance from the individual patient’s perspective. We argue that by adopting the individual patient perspective, the components for further improvement of the existing value frameworks, notably by ASCO, become more self-evident.

Recommendations

Our recommendations are that a value framework focused on the individual HCP-patient interaction can benefit from 3 straightforward, yet important further improvements: (1) use exclusively absolute measures of risk; (2) augment the framework through recognizing that valuation of outcomes by the individual patient has a probabilistic element to it and apply established patient-preference methodology to capture value trade-offs (e.g., per the previously mentioned hopeful gambles
vs. safe bets); and (3) consider losing safety and tolerability parameters for more multidomain, patient-relevant QoL considerations and incorporate evolving progress in this area. We believe that through addressing these aspects, coupled with a cross-functional dialogue of relevant stakeholders, further progress can be made towards a value framework that is even more meaningful to the individual patient.

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