Could QALYs Help in Assessing High-Priced Cancer Treatments?

Other nations use ‘quality-adjusted life-years’ to measure the cost-effectiveness of drugs, but this tool has been anathema in the United States — so far

By Jack McCain

For doctors at Memorial Sloan-Kettering Cancer Center in late 2012, it was an easy call. The drug Zaltrap, new on the market (Bach 2012) for treatment of patients with metastatic colorectal cancer, promised to provide an overall survival benefit of 1.4 months compared with a standard chemotherapy regimen. But so did Avastin (bevacizumab) — and the two drugs had similar mechanisms of action, preventing the interaction of VEGF with its receptors. The chief difference was that Zaltrap, initially priced at $11,000 for one month of treatment, cost more than twice as much as Avastin. So the oncologists decided not to use this costly drug. And from the perspective of the cancer center, the story has a happy ending: The marketers of Zaltrap began offering the drug to hospitals at a 50% discount.

But other comparisons of oncology products are not so straightforward. A new drug may offer a modest improvement in overall survival quality of life in the absence of a survival benefit. What then?

Outside the United States, policymakers turn to a measurement unit called the “quality-adjusted life-year,” (see “What’s a QALY?” on page 33), though with less enthusiasm than in years past to inform decisions on allocating resources to new drugs. And some experts think it may be time for QALY’s American debut.

FIGURE 1
Relationship between quality and quantity of life

Which intervention would you choose? Compared with Usual Care, Intervention A offers shorter length of life but improved quality of life. Intervention B provides higher quality of life than Usual Care but the same length of life; the triangle bounded by the sloping and vertical red lines and the sloping black line represents the incremental gain in quality afforded by Intervention B. Compared with Usual Care, the incremental gain in quality from Intervention B is less than that provided by Intervention A, however. Intervention C provides longer length of life than Usual Care or Intervention A or B but lower quality of life than those interventions or Usual Care. Intervention D initially offers actual improvement in quality of life followed by a steep decline, and although length of life is longer than with any other intervention or Usual Care the quality of life ultimately is greatly diminished.
To quantify value

In an essay in the New York Times, some prominent oncologists and cancer researchers set forth their prescription for improving cancer care (Emanuel 2013). By way of introduction, they said the FDA had approved 13 anticancer agents in 2012, each costing more than $5,900 per month — and that only one offered a survival benefit exceeding six months. The heart of the essay was a set of five recommendations (see box on page 34). Although the word wasn’t used, the thorny issue of value was implicit in each recommendation. Consumers commonly regard high price as an indication of high value whether they’re purchasing wine, automobiles, higher education or, alas, health care goods and services.

Perhaps that shouldn’t be terribly surprising because, as the health economist Tina Shih, PhD, points out, we really don’t know how to quantify value. Shih is an associate professor of medicine at the University of Chicago and director of its Program in the Economics of Cancer.

Health economists have various tools for evaluating interventions (Table 1), the simplest of which, in theory, is cost-minimization analysis. If two different therapies produce the same outcome, you just choose the less expensive one. Such was the call made by the Memorial Sloan-Kettering doctors at

What’s a QALY?

A quality-adjusted life-year is the bidimensional measure used in the form of cost-effectiveness analysis known as cost-utility analysis. QALYs capture quantity and quality of life in a single metric. QALYs are computed by asking patients or, preferably, members of the general public to weigh the utility (i.e., indicate their preference) for being in a given health state by assigning a numerical value to it; the values range from 0 (dead) to 1 (in perfect health). The time spent in the health state is multiplied by its assigned value, and the products are summed. (Some economists maintain that since few people ever report being in perfect health, average health might be a more meaningful upper end of the scale.) In a cost-utility analysis, the next step is to calculate the difference in mean costs between the intervention of interest and its comparator, generating the incremental cost, and the mean effectiveness of the intervention compared to the comparator, expressed as QALYs gained. (In other cost-effectiveness analyses, effectiveness might be expressed as life-years gained or, especially in oncology, by a surrogate outcome such as complete response rate or disease-free survival.) Dividing the incremental cost by the mean effectiveness yields the incremental cost-effectiveness ratio (ICER). In the example below, in which two interventions are compared for one year, the gain in QALYs provided by Intervention A is 0.20, and the incremental cost difference is $10,000, which works out to $50,000 per incremental QALY gained.

Ideally, health economists say, cost-utility analyses should be conducted from a broad societal perspective to capture all the direct and indirect costs and consequences associated with an intervention over the long term, but they frequently are conducted from the narrow perspective of a third-party payer concerned only with direct costs over the short term.

<table>
<thead>
<tr>
<th>Utility weight of health state*</th>
<th>Time spent in health state</th>
<th>Utility weight x time spent</th>
<th>Utility weight of health state*</th>
<th>Time spent in health state</th>
<th>Utility weight x time spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>0.25 y</td>
<td>0.225</td>
<td>0.7</td>
<td>0.25 y</td>
<td>0.175</td>
</tr>
<tr>
<td>0.8</td>
<td>0.25 y</td>
<td>0.200</td>
<td>0.6</td>
<td>0.25 y</td>
<td>0.150</td>
</tr>
<tr>
<td>0.7</td>
<td>0.25 y</td>
<td>0.175</td>
<td>0.5</td>
<td>0.25 y</td>
<td>0.125</td>
</tr>
<tr>
<td>0.6</td>
<td>0.25 y</td>
<td>0.150</td>
<td>0.4</td>
<td>0.25 y</td>
<td>0.100</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>0.750</td>
<td></td>
<td></td>
<td>0.550</td>
</tr>
<tr>
<td>Mean effectiveness</td>
<td></td>
<td>0.200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incremental cost</td>
<td></td>
<td>$10,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incremental cost-effectiveness ratio</td>
<td></td>
<td>$50,000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The health states do not necessarily unfold in the order presented here. The actual order in which they do occur may be important to some patients, however, but a cost-utility analysis will not take this into account.
the time that Zaltrap was introduced. Combining length of life and quality of life in a single metric, the QALY enables comparisons of interventions in disparate diseases. In the U.K., the National Institute for Health and Care Excellence (NICE) mandates use of cost-utility analysis as a tool — but not the sole tool — to determine which interventions should be provided by the National Health Service. It’s a strike against a new intervention if its cost per QALY exceeds £30,000, the upper limit of NICE’s arbitrary range for cost-effectiveness. Shih says QALYs are best employed from a societal perspective, and not for making treatment decisions for individuals with a disease, especially in end-of-life situations.

**Is end of life different?**

Even NICE now makes exceptions for end-of-life treatments, largely in reaction to the furor that erupted in 2008 when it rejected some new cancer drugs because they weren’t deemed sufficiently cost-effective. The next year, NICE made major adjustments (http://bit.ly/nice-EOL), allowing drugs used in end-of-life care to exceed the threshold if the treatment is aimed at a small patient population and extends life by at least three months, compared with the current treatment, in patients whose life expectancy is less than 24 months.

None of the 2012 approvals represents a dramatic breakthrough, such as a new first-line treatment that

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Analyses used in health economics research</th>
<th>Use</th>
<th>Metric</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of illness</td>
<td>Measuring the economic burden of a disease</td>
<td>Costs from perspective of interested party or parties (e.g., society, third-party payer, business, government)</td>
<td>Defining the illness may be complicated; Inclusion of indirect costs generates controversy</td>
<td></td>
</tr>
<tr>
<td>Cost-benefit</td>
<td>Computing total costs and benefits of an intervention</td>
<td>$ gained or lost from the intervention</td>
<td>Difficult to quantify some components</td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Comparing the costs &amp; benefits of interventions not expected to produce the same outcomes</td>
<td>$ per natural unit (e.g., life-years gained, duration of disease-free survival, response rate, mm Hg in BP reduction)</td>
<td>Unit of comparison may not be the most clinically relevant measure</td>
<td></td>
</tr>
<tr>
<td>Cost-minimization</td>
<td>Comparing interventions expected to produce the same outcome (e.g., generic simvastatin vs. branded Zocor)</td>
<td>Price differential</td>
<td>Not easy in most cases to demonstrate clinical equivalence; Limited practical use</td>
<td></td>
</tr>
<tr>
<td>Cost-consequence</td>
<td>Comparing alternative interventions by computing the components of their incremental costs and consequences</td>
<td>List of each component</td>
<td>Doesn’t generate an aggregated result</td>
<td></td>
</tr>
<tr>
<td>Cost-utility</td>
<td>Comparing disparate interventions employed in disparate diseases, for purpose of resource allocation</td>
<td>Incremental $ per QALY compared with alternative intervention</td>
<td>QALYs in different diseases may not be commensurate</td>
<td></td>
</tr>
</tbody>
</table>
adds years to cancer patients’ lives. Instead, they’re for patients already in dire straits — patients with metastatic disease for which second- or third-line treatments no longer are effective. Some of these drugs wouldn’t pass muster with NICE because they serve small populations and don’t extend life by at least three months.

What oncologists think

Even so, a recent survey of U.S. and Canadian oncologists suggests that the majority of oncologists wouldn’t balk at high prices for such drugs (Ubel 2012). When asked what treatment cost per life-year gained represented “good value for money,” about 70% selected an incremental cost-effectiveness ratio (ICER) of $100,000 or less. But when oncologists were randomly presented with hypothetical new drugs for metastatic cancer that cost either $50,000 or $125,000 more than standard chemotherapy costing $25,000, the median increase in life expectancy stipulated by oncologists to justify using the $75,000 drug was six months, which translates into $100,000 per life-year gained. The median survival benefit oncologists selected to support use of the more-expensive drug also was six months, but in this case the cost per life-year gained was $250,000.

Each is the best-case scenario for cost per QALY, because if the time is spent in less than perfect health, the cost per QALY would be even higher.

Although the study shows that oncologists seem to be rather inconsistent and illogical in their approach to the value of their drugs, the authors said their results shouldn’t be taken as criticism of oncologists, for several reasons:

- Oncologists aren’t trained to use cost-effectiveness data in decision-making.
- Oncologists aren’t comfortable using such data.
- Oncologists usually aren’t aware of the cost of the drugs they’re prescribing (other studies show they are concerned about the amount of a patient’s copayment, which in itself can adversely affect compliance with therapy).
- Oncologists are taught to just let policymakers deal with these matters.

In another study, oncologists at Massachusetts General Hospital and the Dana-Farber Cancer Institute were asked to identify the minimum survival benefit they’d need to prescribe a hypothetical new treatment for metastatic lung cancer if the new treatment cost $70,000 per year more than the standard-of-care treatment and if there was no difference in quality of life between the standard and the new

![Figure 2](image-url)

**FIGURE 2**

Gain in life expectancy needed to justify use of hypothetical drug costing $70,000 per year more than standard care; incremental cost-effectiveness ratios

The dollar amount above each column shows the implied incremental cost-effectiveness ratio (ICER) for each response, as provided by academic oncologists in Boston when asked to attach an outcome to a dollar amount ($70,000 more per year than standard care). The median ICER was $280,000 and the mean ICER, which excluded the “1 day” response, was $319,000. (A study of the preferences of patients with metastatic cancer suggests that they are willing to pay comparable amounts per year of life gained [Seabury 2012].) When asked to attach a dollar amount to an outcome, however, 70% of U.S. oncologists responding to a national survey indicated $100,000 or less per life-year gained was a reasonable definition of “good value for money” or cost-effectiveness (Neumann 2010a). In a survey of U.S. and Canadian oncologists, when asked what treatment cost per life-year gained represented “good value for money,” about 70% of the physicians selected an ICER of $100,000 or less, but when the question was framed differently, many were satisfied with much higher ICERs (Ubel 2012).

SOURCE: Nadler 2006
treatment (Nadler 2006). The responses ranged from one day (ICER of $25.6 million) to one year or more (ICER of $70,000), with the median and mean responses being $280,000 and $319,000 respectively (Figure 2).

**Suspicion**

In the United States, QALYs often are regarded with suspicion, so much so that the Affordable Care Act forbids the Patient-Centered Outcomes Research Institute to use the cost per QALY “or similar measure that discounts the value of a life because of an individual’s disability as a threshold to establish what type of health care is cost effective or recommended.”

Peter Neumann, ScD, professor of medicine at Tufts University School of Medicine and director of Tufts’ Center for the Evaluation of Value and Risk in Health, speculates that the ambiguous language of this passage might permit ICERs using cost per QALY to be calculated but not compared with a threshold, but that it might also be construed as a broader ban on cost-utility analysis (Neumann 2010b). (Neumann has studied QALYs extensively and published numerous scholarly articles about their use in oncology among other areas.)

The fact that legislators saw fit to insert language in the Affordable Care Act to ban the use of QALYs may seem unfortunate and bizarre in a nation where there’s so much talk about the high costs of health care. Whatever the reasoning behind the legislation, it runs counter to what most oncologists apparently want. In a national survey of U.S. oncologists, 80% “strongly or somewhat agreed” that more use of cost-effectiveness data is needed in coverage and payment decisions for cancer drugs, and that more government research is needed on the comparative effectiveness of cancer drugs (Neumann 2010a). Well, good luck with that.

But while the oncologists said they’d like to see the government provide more comparative effectiveness research, only 21% thought government should determine whether a drug provides good value — and a mere 6% thought insurance companies should do so. Instead, they wanted value determinations to be made by physicians (60%), not-for-profit organizations, (57%) and patients (37%). Taken together, these studies suggest that if oncologists want to make value-based treatment decisions, at least some of them need guidance in evaluating cost-effectiveness data.

“QALYs are easy to criticize, but it’s hard to capture anything with a single number,” Neumann says. He cites the Dow Jones Industrial Average and the measurement of snowfall by inches as common metrics that tell us something interesting but hardly tell us everything needed to adequately assess the phenomena in question.

Likewise, he says, “The QALY has a place as a crude but imperfect measure of value. I recoil when it’s used rigidly.”

From the perspective of pharmaceutical companies, an objection to QALYs is that overreliance on them could stifle innovation. According to this argument, some drugs — especially first-in-class agents — merit a high price and a high cost per QALY in order to spur further research. Herceptin (trastuzumab), for example, was initially approved as first-line therapy for metastatic breast cancer, and for that indication its cost per QALY gained was calculated as at least $125,000. That’s far above the conventional threshold. But in the adjuvant setting, its cost per QALY was found to be only $26,000. Had the drug been rejected initially because of an unacceptably high cost per QALY, the opportunity to study it in the adjuvant setting might never have arisen. But Shih says such pharmacoeconomic analyses should be interpreted cautiously, because they often are just retrospective mathematical models that are subject to manipulation.

**Comparisons are difficult**

In the case of Zaltrap, oncologists had no need to call on QALYs to determine that the initial price of the new drug was far too high. Its value relative to a competing product was immediately apparent because the efficacy and safety of each drug were regarded as equivalent, and market forces (lack of demand) soon led to a downward adjustment in price.

Comparisons of other cancer drugs tend to be far more difficult because the products aren’t equivalent, in which case QALYs may be one tool that complements others to help policymakers, physi-
cians, and patients determine which drug offers the best value.

People like the freedom to use whatever drug they want, says Shih, but at some point we have to face the reality that resources are limited. If we don’t want to use cost-effectiveness analyses to allocate resources, what process are we going to use, she asks, other than the random process employed right now?

Neumann says that to reject QALYs in the absence of a better metric is to implicitly argue that we’re better off if the trade-offs revealed by QALYs remain hidden. Still, in the current environment, one person’s quest for value may be perceived and portrayed by someone else as the imposition of rationing. NCI

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For further reading

TABLE 3
Common arguments against using QALYs in end-of-life situations

<table>
<thead>
<tr>
<th>Argument against QALY</th>
<th>Counterargument</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because it includes a time element, a QALY is inappropriate if an intervention provides no survival benefit</td>
<td>An intervention can enhance life (i.e., generate a gain in QALYs) even if it doesn’t extend life</td>
</tr>
<tr>
<td>2. In comparison with other dimensions of quality of life, health status diminishes in importance at the end of life</td>
<td>• There’s no reason non-health domains can’t be incorporated in QALYs, if it is decided that they should be incorporated • The (not-so-simple) solution is finding out what is important to people at the end of life and measuring it</td>
</tr>
<tr>
<td>3. Patients’ preferences for health states aren’t reliable at the end of life because their preferences change over time</td>
<td>Instability of preferences becomes a problem only when patients’ preferences are used, so a practical solution is to use the preferences of the general public</td>
</tr>
<tr>
<td>4. When death is imminent, death is an invalid anchor point for preference-based measures of health status</td>
<td>• Problem diminishes when the general public is used instead of patients as the source of preferences for health states • However, this argument does have merit</td>
</tr>
<tr>
<td>5. People value life differently at the end of life in comparison with other life stages</td>
<td>• This is the argument behind NICE’s decision to allow exceptions for end-of-life treatments that exceed the established cost-effectiveness threshold but meet certain criteria • It has not yet been demonstrated that individuals and society value end-of-life time greater than time at other stages of life</td>
</tr>
<tr>
<td>6. Reliance on QALYs leads to rejection, on cost-effectiveness grounds, of some interventions that are acceptable to patients and the public</td>
<td>• Phenomenon is not unique to end-of-life care • Since thresholds are political determinations, thresholds are subject to political modification</td>
</tr>
</tbody>
</table>

Source: Round 2012

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