How Cancer Patients Value Hope And The Implications For Cost-Effectiveness Assessments Of High-Cost Cancer Therapies

ABSTRACT Assessments of the medical and economic value of therapies in diseases such as cancer traditionally focus on average or median gains in patients’ survival. This focus ignores the value that patients may place on a therapy with a wider “spread” of outcomes that offer the potential of a longer period of survival. We call such treatments “hopeful gambles” and contrast them with “safe bets” that offer similar average survival but less chance of a large gain. Real-world therapy options do not have these stylized forms, but they can differ in the spread of survival gains that patients face. We found that 77 percent of surveyed cancer patients with melanoma, breast cancer, or other kinds of solid tumors preferred hopeful gambles to safe bets. This suggests that current technology assessments, which often determine access to such cancer therapies, may be missing an important source of value to patients and should either incorporate hope into the value of therapies or set a higher threshold for an acceptable cost-effectiveness ratio in the end-of-life context.

Controversy continues to surround approaches to measuring the value of health care. The stakes are high for payers, patients, providers, and drug and medical device manufacturers. Nowhere is this lack of consensus more apparent than in the treatment of cancer.

Consider, for example, the UK National Institute for Health and Clinical Excellence. This “health technology assessment” agency assesses the medical and economic value of therapies, and it makes recommendations that may guide coverage decisions within the UK National Health Service. In response to pressure from patients and policy makers, the agency recently carved out an exception from its standard procedures by allowing a more generous threshold for therapies used when life expectancy is short. This carve-out could apply to some cancer therapies.

To date, much of the methodological debate regarding the value of oncologic therapy has justifiably focused on choosing the right value for an additional month of survival, often accounting for the quality of life associated with the additional month. The value of an improvement in health is an important issue, but less attention has been paid to the issue of how to quantify the magnitude of the improvement. This latter issue is also important because the total value of a therapy is typically equal to the value placed on improved health—such as a one-year gain in survival—multiplied by the magnitude of the improvement in health—such as the average gain in survival from a therapy.

Researchers have generally assumed that patients and policy makers care about the average or median gain in survival, or quality-adjusted survival. However, economists, psychologists, and other social scientists have long understood that people care about risk. For example, handing $100 to a consumer is different from offering a coin flip that earns $200 for heads but nothing...
for tails. Even though the coin flip has an average or expected value of $100—a one-half probability of coming up heads multiplied by $200—which is equal to the handing over of $100 cash, most consumers will not view it the same way as a guaranteed payment of $100.

In the health technology assessment context, this observation implies that patients may care about more than just the average or median survival gains associated with a therapy. They may also care about the variability, or “spread,” of survival gains around the average gain. For example, patients may value the “hope” of a large survival gain, independent of a therapy’s average gain. Therefore, in this study we took an empirical approach to measuring the value that patients with a limited life expectancy placed on the “spread” of survival outcomes, above and beyond the average survival gain associated with a cancer therapy.

Conceptual Background
As a simple motivating example, consider one therapy—called a “sure bet”—that promises patients exactly eighteen months of additional survival. Now consider an alternative—called a “hopeful gamble”—that promises a 50 percent chance of thirty-six months of additional survival but also a 50 percent chance of no additional survival, or zero additional months. Both alternatives offer eighteen months of expected gain but may be viewed differently by patients. The hopeful gamble provides a chance of a bigger upside but also a worse downside. In this sense, it involves more risk for the patient.

Consumers typically dislike risk. This explains, for example, why they demand insurance against risks to health, property, and life. Yet a long-standing conjecture in the economic analysis of risk is that a consumer who is risk-averse under normal circumstances will become risk-prefering if he or she has relatively little to lose. This would predict that extreme poverty would motivate people to take risks through criminal behavior or through more innocuous activities such as playing the lottery. Intuitively, the “downside risk” of losing a gamble is less costly to a person in dire circumstances, when things “cannot get much worse.”

Applied to the health care context, this conjecture suggests the possibility that people in decent health may dislike the risks associated with medical care, such as potential side effects from the treatment following a possible false positive on a diagnostic test. However, patients facing a fatal disease or with relatively short remaining life expectancy may prefer a hopeful gamble to a sure bet. Such patients may be willing to accept a risk of greater short-term mortality, in exchange for a chance at a large and highly meaningful gain in survival. Put more colloquially, a very sick patient may opt to “swing for the fences,” since “striking out” does not make her much worse off than she already is.

In summary, there is an empirical question: Do patients near the end of life like or dislike therapies with greater spread in survival outcomes? To address it, we investigated whether cancer patients preferred sure bets or hopeful gambles that were drawn from real-world examples in the treatment of melanoma and metastatic breast cancer.

Study Data And Methods
To provide real-world context for our study, we focused on two clinical contexts in advanced cancer: metastatic malignant melanoma and metastatic breast cancer. Real-world therapy options do not have the stylized form of a sure bet versus a hopeful gamble, but they do differ in the risk, or spread, that patients face when assessing their likely survival outcomes.

Consider first the case of the chemotherapy drug ipilimumab (Yervoy), which in its pivotal clinical trial was compared to glycoprotein-100 (gp100) in melanoma patients with unresectable tumors—those that cannot be removed surgically—or with metastatic disease. Compared to gp100, ipilimumab raised median survival for melanoma patients by approximately 3.5 months. This is not an insignificant gain in median survival by the standards of oncology innovation, but it is also not extraordinary by any measure. However, more than 90 percent of the trial patients on gp10 were dead within thirty-six months of initiating therapy (Exhibit 1).

In contrast, one out of five ipilimumab patients were still alive after forty-four—even fifty-four—months. The salient question is whether patients view that additional one in five chance at long-term survival as equivalent to a 3.5-month increase in median survival, or whether they view it as much more valuable.

Consider the complementary example of treatment for metastatic breast cancer that has shown resistance to drug treatment. In particular, in a recent clinical trial, patients treated with ixabepilone (Ixempra) plus capecitabine (Xeloda) had a one in ten chance of living past forty-eight months (median survival of 12.9 months). Do patients view this profile with a possibility of long-term survival as different from a hypothetical, more certain profile with a similar average survival but no chance of living four more years?

Testing this hypothesis with marketplace data is difficult because therapies differ along a variety of attributes, not just spread in survival out-
comes. For instance, one therapy may be a hopeful gamble compared to an alternative, but it may also involve fewer or milder side effects and may be covered more generously by insurance. It might be possible to tease out attitudes toward risk with enough data on real-world use of therapies that differ in ways including the spread of outcomes or side effects. But a more direct approach suffices for a "proof of concept" to assess whether patients do care about risk.

**SURVEY METHODS** We developed a survey instrument that isolated the hopeful aspect of therapy choices that resembled the melanoma and breast cancer treatment contexts discussed above. One survey arm presented participants with a hypothetical scenario for the treatment of advanced melanoma. The other focused on the treatment of metastatic breast cancer.

Participants were shown key features of the survival profile of the hopeful therapies, including average survival and the likelihood of dying within specific time frames, calibrated to the clinical evidence described earlier. In each survey arm, participants compared the hopeful therapy with a hypothetical therapy that provided the same average survival, but with death occurring with 100 percent certainty at the average survival time—eighteen and twenty-four months in the breast cancer and melanoma contexts, respectively. Participants were asked which they preferred. These scenarios are shown in the online Survey Appendix.

The survey then asked how much patients or their families would be willing to pay for their preferred therapy, rather than the alternative. We used the "payment card" format, in which a participant was presented with a set of possible values and asked to identify the maximum value that would willingly be paid. Payment cards help minimize nonresponse, given the yes-or-no questions about willingness to pay. Payment cards also avoid biases from other approaches. For example, the presentation of a yes-or-no question about a particular willingness-to-pay amount can be confounded by respondents’ tendency to answer "yes.”

Interviews were conducted face-to-face, as recommended by an expert panel that assessed the reliability of alternative methods for surveying individuals about their willingness to pay for goods. This expert panel has been influential in the design and implementation of such surveys, including studies of pharmaceutical treatments for cancer. This approach limits bias from the nonrandom participation that confounds other methods, such as mailed surveys.

The survey contained additional modules on cancer history, such as tumor type, time since diagnosis, disease stage, and treatment history; other patient characteristics such as sex, age, race or ethnicity, income, marital status, family size, and insurance coverage; and comprehension of the term median survival. The survey design was approved by an Institutional Review Board.

The survey sample included 150 cancer patients undergoing treatment, whether radiation, chemotherapy, or "watchful waiting.” Surveys were conducted during January–March 2011 at five sites within a national network of independent, community-based oncology practices. Sites were located in all four US census regions, and at least 15 percent of patients were drawn from each region to achieve a degree of geographic balance. Forty-seven breast cancer patients were assigned to the breast cancer arm, while twenty patients with melanoma were assigned to the melanoma arm. A third group of patients had a diverse set of “solid” tumors; for example, lung cancer is a solid tumor, while leukemia is not, because the latter afflicts blood cells. This third group of patients was randomized into the two survey arms to balance their subsamples. Disease stage was obtained for patients with breast cancer; twenty "late-stage” patients (stage IV breast cancer, based on American Joint Committee on Cancer staging) were sampled. Additional details are provided in the online Survey Appendix.

**ANALYSIS** In analyzing survey responses, we used interval regressions because participants reported their willingness to pay on the payment cards within ranges. The final analysis accounted for patients’ age, sex, race or ethnicity, tumor type, and income. Willingness-to-pay estimates changed little as these covariates were added. Our analysis methods and results are described in detail in the online Technical Appendix.

**Study Results** Importantly, 77 percent of the patients surveyed preferred a hopeful gamble to the sure bet, even though the two provided the same survival, on
average (Exhibit 2). Of the patients in the melanoma arm, 71 percent would give up the chance of living two years for sure in return for a 20 percent chance of living for at least four and a half years. Of the patients in the breast cancer arm, 83 percent would give up the chance of living one and a half years for sure to have a 10 percent chance of living four years or more.

Another analysis, not reported here, found that five percentage points of the twelve-point difference between the breast cancer and melanoma survey arms (83 percent minus 71 percent) might result from the overrepresentation of patients with other kinds of solid tumors in the melanoma arm (the effect was not statistically significant after adjustment for multiple comparisons).

When shown the payment cards, some patients were willing to pay substantial amounts for a hopeful therapy (Exhibit 3). One-quarter of the patients in the melanoma arm were willing to pay at least $45,000 to get the hopeful gamble instead of the sure bet, while a quarter of the patients in the breast cancer arm were willing to pay at least $90,000.

Based on the statistical analysis, patients’ average willingness to pay for a hopeful therapy was $54,362 (95% confidence interval: $33,501, $75,673). In terms of the variability of survival times with the two hopeful therapies, the average patient would pay $36,305 for a one-year increase in the standard deviation of survival.

The relationship between income and willingness to pay for a hopeful therapy is shown in Exhibit 4. People in the highest quartile would pay more than ten times as much for a hopeful therapy as patients in the lowest quartile.

**Discussion**

We surveyed cancer patients about their willingness to pay for therapies that provide a hopeful gamble versus a safe bet. The hopeful gamble provides a greater chance at a large survival gain, but also the possibility of a worse downside. Treatments for metastatic melanoma and breast cancer served as case studies.

Patients differed in their preferences for risk taking, as one might expect. However, the vast majority of patients seemed to prefer the hopeful gambles to the sure bets. It seems plausible to assume that cancer patients can accurately report their preferences across two types of treatment options because ostensibly these people have experience in making clinical decisions about their treatment.

Although the survival scenarios presented to patients avoided statistical jargon, a subsequent survey module assessed patients’ comprehension of the term *median survival*. In a sensitivity analysis, the 27 percent of cancer patients who correctly interpreted this term had a higher willingness to pay for a hopeful therapy, although the difference was not statistically significant.

Altogether, these results suggest that most cancer patients may prefer a therapy with the possibility of a large survival gain, even if the therapy’s average or median survival is similar to that of alternative therapies. Patients facing other fatal diseases might share such a preference; evidence from other contexts would be welcome in reinforcing and extending the base of evidence on this point.

It may require stronger assumptions to believe that patients can accurately disclose the degree to which they prefer one therapy over the other, in the form of a monetary value. Nonetheless, our results indicate that this preference is substantial for many patients, and that—not surpris-
ingly—higher-income patients are willing to pay more than their lower-income counterparts are. Interestingly, income was not related to the probability of preferring the hopeful gamble. This finding suggests that the choice of therapies is independent of income but that the willingness to pay for the chosen therapy is not.

Do patients place distinct value on the chance of a long-term survival benefit? Our results suggest that they might place independent value on a chance at a long-term survival benefit, above and beyond its contribution to average survival. That is, patients might view two therapies with equal average survival as unequal, if one affords a greater chance of a long-term benefit. Although our findings are intriguing and suggestive in this respect, questions remain for future research.

First, we performed a stylized comparison between a therapy with no spread in survival outcomes and one that involves a large spread. It would be useful to know whether our results extend to circumstances in which patients choose between two therapies that both involve some spread in outcomes but differ in the degree of spread. In other words, were our results shaped by the views of patients who particularly disliked therapies that promised an absolutely certain length of survival?

Second, it is also important to assess whether these preferences manifest themselves in marketplace behavior—that is, in the psychology and decisions of actual market participants. Typically, economists prefer to rely on real-world decisions as a way to understand preferences, rather than on direct questions about preferences. Survey participants may have less incentive or ability to disclose preferences accurately than real-world actors. To be sure, some creativity and analytical structure will be required to make inferences about the value of hopeful gambles in real-world data. On the other hand, real-world evidence would not be confounded by problems that can afflict face-to-face surveys, such as a temptation among respondents to answer a question in a way that others may view favorably.13

Assuming that these early results bear up under the scrutiny of future research, it is instructive to look ahead to their policy implications. If patients care about long-term survival prospects, not just average survival, this suggests the need to incorporate long-term benefits as a unique consideration in health technology assessment for oncology treatment.

Elsewhere we have argued for a two-step approach to health technology assessment.14 The first step is a conventional health technology assessment process based on average survival and conventional values of an extra year of life, often adjusting for the corresponding quality of life. The second step incorporates special considerations, like unmet need, terminal care, and perhaps also long-term survival benefits.

Although highly simplified, this provides a feasible way of incorporating the value of hopeful gambles into standard health technology assessment procedures. Specifically, health technology assessment bodies such as the UK National Institute for Health and Clinical Excellence or public and private health policy decision makers in the United States could either incorporate hope into the value of therapies or set a higher threshold for an acceptable cost-effectiveness ratio in the end-of-life context. Value-based benefit design might also account for the importance of hope to patients.

Of course, these policy implications rest upon the assumption that patients understand and can act upon their own preferences. It is possible that patients suffer from various cognitive biases—for instance, optimism bias that causes them to believe they will systematically be luckier than the average person. In this case, the preferences they disclose might not be internally consistent. If true, this makes policy analysis of all kinds more difficult. The underlying problem is that if patients do not know what is best for themselves, there is no way to make them better off both in fact and in their own minds.15

Abstracting from such “metaphysical” considerations, our research suggests that there may be a need to broaden the horizons of health technology assessment when it comes to measuring health gains. Spread in outcomes is only one
aspect of the issue. Patients may view treatments differently at different ages, in different family circumstances, or from other perspectives.

This analysis points to the larger ideal—that value should be defined from the viewpoint of the patient. This is a type of “golden rule” of paying for care that patients would value, if they made the treatment decision themselves.

In more technical terms, economic theory implies that treatments should be allocated to patients who value the treatment more than it costs. Ultimately, this perspective avoids the problems of paternalism, which values therapy according to external benchmarks that exist independently of an individual patient. Health insurance interposes a public or private payer between a patient and the choice of therapies, yet it does not undermine the fundamental logic that patients should receive the care that they themselves think is most valuable.

NOTES

7. To access the Appendix, click on the Appendix link in the box to the right of the article online.
9. This format has also been used to determine the value of docetaxel to ovarian cancer patients. See Dranitsaris G, Elia-Pacitti J, Cottrell W. Measuring treatment preferences and willingness to pay for docetaxel in advanced ovarian cancer. Pharmacoeconomics. 2004;22(6):375–87.

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Darius Lakdawalla is director of research at the Leonard D. Schaeffer Center for Health Policy and Economics at the University of Southern California. In this month’s Health Affairs, Darius Lakdawalla and coauthors consider what the value of hope is to terminally ill cancer patients and how—if at all—that value should be incorporated into cost-effectiveness assessments of cancer therapies. The authors surveyed how patients with melanoma or breast cancer would react to two therapy choices, one guaranteeing a modest length of survival and the other offering a 50 percent chance of a substantially longer period of survival but also a 50 percent chance of no additional survival. The majority of patients preferred the latter option, underscoring the fact that “cancer patients value even a small chance
at a large survival gain,” in the words of Lakdawalla, director of research at the Leonard D. Schaeffer Center for Health Policy and Economics at the University of Southern California (USC). The authors assert that this attitude of hopefulness is an important source of value to patients and should be taken into account in cost-effectiveness assessments.

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