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New Cost-Effectiveness Methods to Determine Value-Based Prices for Potential Cures: What Are the Options?

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ABSTRACT

Evaluating different approaches to assessing the clinical effectiveness and value of potential cures will be essential to arm the policymaker, payer, and manufacturer communities with a platform that can reward innovation while supporting a sustainable health insurance system. Potential cures will accentuate concerns about substantial uncertainty in long-term outcomes. They will also focus attention on whether broader elements of value need to be incorporated and whether specific social values have a special place in evaluations of potential cures. In addition, the large magnitudes of potential health gain and cost offsets may require new methods before translation into value-based price recommendations. This article analyzes the challenges and presents several options to modify the conduct and presentation of cost-effectiveness analyses to ensure they provide policy-relevant assessments of the value of potential cures.

Keywords: health policy, methods, pharmacology/pharmacotherapy, unit costing, utility assessment.

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Introduction

Public and private insurers across the world are rapidly approaching the time when they will be called upon to manage a growing number of drugs that, with only a single dose or short course of therapy, offer the potential to cure a wide range of illnesses. Just within the past year, three treatments have received regulatory approval in the United States—a genetic therapy for a rare form of childhood blindness, and two chimeric antigen receptor T-cell therapies for leukemia and lymphoma—all of which boast early evidence that suggests some patients may receive durable lifetime benefits, even complete cures.[1,2] There is great excitement about the potential for these types of treatments to bring hope and miraculous advances to patients and families who have long suffered without adequate options.

The global innovation pipeline now includes many more potential cures for rare, genetically based conditions such as hemophilia, along with treatments for more common conditions such as sickle cell disease.[3] Life science companies, investors, and insurers all expect that these treatments will command high prices—very high prices. The first genetically based therapies approved in the United States have been priced between $475 000 and $850 000, and health system insurers and other policymakers are worried that, as a growing number of potential cures are introduced, their aggregate cost will severely strain the affordability of healthcare.[3–5] No matter how desirable these treatments may be clinically, health insurance systems of today appear ill-prepared to face the challenge of assessing and paying for the growing number of potential cures that will soon become available.[6]

Policy analyses of this challenge have largely focused on developing new ways to pay the extremely high prices of one-time or short-term treatments that provide the possibility of a lifetime of benefit. Solutions explored have included various ways to link payment to patient outcomes and to amortize one-time high prices by stretching out payment over many years.[4,6,7] But this will not be sufficient. Inseparable from the problem of paying for cures is the challenge of evaluating their clinical effectiveness and cost-effectiveness as part of determining a "reasonable" price. Even if very high prices can be amortized over many years and some form of retroactive discount or refund is given should patients not be cured, that still leaves the question of how to determine what a fair, reasonable, value-based price should be for a potential cure.

The fundamental methodology to generate information to guide the calculation of prices aligned with patient benefit, or "value-based" pricing, has traditionally been cost-effectiveness analysis (CEA). Despite perennial questions about how to combine CEA results with other considerations, including short-term affordability, prices associated with certain willingness to pay thresholds as calculated in CEA remain the foundation for discussion of value-based prices for emerging therapies.

This article will describe the major methodological challenges in employing CEA to suggest value-based price levels for potential cures. Among those challenges, one in particular will be

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emphasized—the challenge presented by the way that standard CEA translates very substantial lifetime health gains and cost offsets into recommended value-based prices. The argument of this article will be that new methods options should be rapidly debated and tested because new options are urgently needed for CEA to remain relevant in discussions of how to determine value-based prices for potential cures.

Challenges in Calculating a Value-Based Price for a Potential Cure

There are several important methodological and ethical issues that arise in the evaluation of other types of treatments that can appear in a concentrated and cumulative manner when assessing potential cures. These include the following:

1. *How should value-based prices for potential cures reflect substantial uncertainty regarding clinical effectiveness owing to limitations in study design, outcome measures, and the size and duration of clinical trials?*

The vast majority of potential cures in the pipeline are targeted at serious or life-threatening conditions with a known genetic cause. These conditions commonly affect a small population, thereby qualifying as an orphan or even an ultra-orphan condition.[8] The combination of small population sizes and serious and progressive symptoms can raise ethical and practical barriers to using randomized controlled trials (RCTs) in the early evaluation of new treatments. Single-arm trials, or randomized controlled trials with early crossover are therefore likely to be common standards for regulatory approval, and the risk may be high that selection bias or other biases inherent in these study designs may undermine the validity of the results. Other factors that can complicate the generation of robust evidence include the lack of standard patient-centered outcome measures or validated surrogate measures; a lack of standardization of "usual supportive care"; and novel mechanisms of action and therapy delivery techniques that raise questions about the long-term safety and durability of any early clinical benefits.[3,4]

None of these elements that are likely to contribute to a higher degree of uncertainty about the clinical effectiveness of potential cures can be routinely avoided; instead, they must be managed transparently and consistently. Over many years methodological research has refined various methods to display uncertainty in cost-effectiveness findings, but it remains unclear what the best options are for empirically capturing the uncertainty inherent in the evidence on potential cures and reflecting it in the presentation of a recommended value-based price. This should be an active area of future research and policy development and will ideally include the participation of all stakeholders.

2. *How should value-based prices for potential cures reflect social values related to treatments for very severe conditions, rapidly fatal conditions, rare conditions, illnesses that afflict children, and conditions that have a high lifetime burden of illness?*

As long as CEA has been used to help assess the "value for money" of new interventions, questions have been raised about whether and how to integrate into those judgments important ethical intuitions or "social values" that are not represented in the basic utilitarian framework reflected in incremental cost-effectiveness ratios. The most common social values considered by HTA groups and insurers relate to severity, rarity, extending life near the end of life, lifetime burden of illness, and involvement of children. In most HTA organizations, rare and particularly ultra-rare conditions are evaluated using a different process and, by extension, weighting of social values.[9,10]

It is likely that potential cures will often raise heightened questions about the role of social values in judgments of a fair value-based price. Most potential cures will involve considerations related to most or all of the following elements: severity, rarity, end of life, lifetime burden of illness, and involvement of children. Future research and policy development will therefore need to continue to explore this issue, with one common goal always being to maximize the transparency for decision makers of how social values are—or are not—included in any recommended value-based price for a potential cure.

3. *How should value-based prices for potential cures reflect uncertainty regarding inclusion of additional elements of value that may be important for potential cures, but which are not part of standard cost-effectiveness methods?*

In addition to the social values described above, active debate continues regarding the number and type of additional dimensions of value that some have proposed should be systematically considered in the evaluation of a new therapy. For example, it has been suggested that there may be intrinsic psychological benefits to patients of feeling "cured" that are not captured in the QALY.[11,12] ISPOR's white paper on value assessment framework also suggests that there are reasons to consider additional dimensions of value for all treatments, including real option value, the value of hope, and insurance value—none of which are captured by the quality-adjusted life year (QALY).[13] The ISPOR paper recognizes, however, as did the recommendations of the Second Panel on Cost-Effectiveness, that these additional elements of value remain controversial, and methods for empirically integrating them into a CEA are not well established.[13,14]

Potential cures seem likely to trigger enhanced consideration of these additional elements of value. Nevertheless, inclusion of any of these additional elements of value would raise fundamental problems of how to measure them and whether these other types of value can be included without assuming that they apply equally to other healthcare services or opportunities for social spending outside the health system. Thus, it would be very difficult to determine how the incremental cost-effectiveness ratio (ICER), or range of ICERs used for generating value-based price recommendations, should be changed to reflect the inclusion of types of value that would seem only to increase value-based prices without addressing the opportunity costs involved.

4. *How should value-based prices for potential cures reflect magnitudes of lifetime health gains and cost offsets that are far beyond those generated by traditional therapies?*

Potential cures for serious diseases offer hope for spectacular lifetime health gains. For conditions that appear in childhood and which are rapidly fatal, such as certain cancers, metabolic disorders, and other genetic abnormalities, true cures could add 50, 60, or 70 years or more of healthy life for all patients treated. By itself, a health gain of this magnitude could raise questions about the relevancy of the use of standard ICERs to suggest value-based prices. For a cure that generated 50 additional QALYs, even if there were no healthcare or societal cost offsets produced by the cure (which would be highly unlikely), using an ICER of $100 000 per QALY would suggest a value-based price of $5 million for this therapy. Interestingly, this price and others suggested by using an ICER of $100 000 per QALY for QALY gains in the range of 50 to 70 for all patients treated approximate the value of a "statistical life"

used by some nonhealth authorities in the United States.[15] Thus, $5 million for this therapy might be consistent with other benchmarks and could serve as the basis for initial consideration of a value-based price. But pricing a potential cure at this level in today's economic environment might also lead many stakeholders and policymakers to reject the use of CEA entirely as a guide for reasonable pricing. Other approaches to understanding how CEA methods can be adapted to provide additional perspectives on value-based pricing would enrich the societal dialogue on this issue.

Even greater difficulties could arise in the more likely context of establishing a value-based price for a cure that does promise substantial—and potentially enormous—lifetime cost offsets. One extreme but useful example to consider would be a one-time therapy providing a cure for patients with hemophilia A. In a recent HTA review from the authors' organization, the Institute for Clinical and Economic Review (ICER), the new drug emicizumab (Hemlibra®, Genentech-Roche, Basel, Switzerland) was compared with usual best care for patients who require prophylaxis with therapies known as bypassing agents.[16] These bypassing agents are so expensive that the economic model developed for this report estimated cumulative long-term costs of treatment for patients receiving usual care to be $90 million to $99 million. It was therefore not a great challenge for emicizumab, which is not a cure but greatly reduces the need for bypassing agents, to be shown as cost-saving even at an annual price of $475 000. For hypothetical purposes, even if it were assumed that a true cure for these patients produced no additional QALYs, the standard value-based price (excluding discounting) would begin at $90 million. We believe that few would disagree that outcomes-based contracts and amortization are not the policy solutions for a treatment price of $90 million. The problem is not the payment mechanism—it is the price—and we believe that any methodology suggesting a price of this magnitude will automatically consign itself to be irrelevant for policy making.

So, what are the potential solutions that should be explored? The ICER includes an analysis of the potential budget impact over 5 years for new treatments and has adopted a threshold for that budget impact that would represent an "affordability and access alert" for policymakers, but it is not used to modulate the suggested value-based price based on standard cost-effectiveness approaches. Using some explicit threshold for short-term affordability could be used by policymakers as an implied or true cap on pricing, but doing so would ignore the important benefits of having a one-time treatment that produces a lifetime of health benefits. Therefore, we believe that for potential cures the standard way CEA is used to suggest value-based price recommendations at willingness-to-pay thresholds needs to be adapted in some way.

We propose consideration of four basic approaches. The first of these would be to adopt a sliding scale for the ICER related to potential cures. For example, if the standard ICER used to generate value-based pricing is $100 000 per QALY, potential cures that generate more than some specific threshold of QALY gains, cost offsets, or a combination of both, could be evaluated using lower thresholds such as $50 000 per QALY. Eligibility for lower ICERs could also be triggered by some magnitude of projected short-term budget impact if standard ICERs are used.

The major advantage of a sliding scale is the ability to create relatively clear rules for deciding when the value-based pricing for potential cures will be done using an alternative approach. Nevertheless, no matter how low the alternative ICER threshold is set, therapies with substantial lifetime cost offsets would still be priced at extremely high prices. The hypothetical cure for hemophilia A, assuming no QALY gains, would still be priced at $25 million using a $25 000 per QALY threshold. Policymakers might find a recommendation of that "lower" price still too extreme to be helpful.

A second adaptation that could be considered for potential cures is to disallow full credit for cost offsets if the services that are no longer required with a cure are themselves not cost-effective, that is, priced above the relevant ICER threshold compared with no treatment. This is easy to imagine in cases such as cancer, where prices for current treatment in the United States often (greatly) exceed traditional cost-effectiveness thresholds between $50 000 and $150 000 per QALY. In the modeling of a potential cure for a cancer whose current treatment is priced at a level commensurate with an ICER of $200 000 per QALY, it is possible for an adapted approach to "reprice" the cost offsets of a cure to whatever the cost would be if current treatment were repriced so as to meet a lower cost-effectiveness threshold.

A third alternative approach to standard CEA calculation of a value-based price for a potential cure would be to cap the price at the willingness to pay for the estimated QALYs gained, no matter how large any cost offsets might be. This approach is demonstrated in two hypothetical cure scenarios presented in Tables 1 and 2. The first scenario evaluates different pricing approaches for a new cure of a fatal disease of a 5-year-old child who would die in 10 years with best current treatments available. Assuming a 50 QALY gain for each individual, a willingness to pay threshold of $100 000 per QALY, and a cost of current treatment of $200 000 per year, the standard value-based price calculation for this cure would be $5 million for the QALY gain (50 years × $100 000 per QALY) plus $2 million for the cost offset (10 years of avoided usual therapy at $200 000 per year), for a total value-based price of $7 million. If the price were capped at the price component owing to added QALYS, the value-based price would be held to $5 million. Table 2 shows a different scenario: a new cure of a nonfatal but disabling disease of a 15-year-old individual who gains 0.2 QALYs per year in improved quality of life over the ensuing 50 years. In this case, capping the price at the QALY-gain component of a value-based price reduces the price even more substantially from that suggested by a standard calculation. Interestingly, and perhaps counterintuitively for some, the higher value-based price using a standard calculation is for the cure of a nonfatal chronic illness ($11 million) rather than a cure for a fatal illness of children ($7 million), even if the usual annual costs of care for both conditions is exactly the same. For many policymakers, both figures are so high as to be risible.

The "QALY-cap" approach has the merit of assigning full value to the therapy for its health benefits. Some might also view it as promoting equity in that prices would reflect a possible social value that the price of a cure for one person should not be worth more than that for another just because one person's condition is currently very expensive to treat. Pricing for a cure for blindness, which has almost no health system costs, and a cure for hemophilia could be viewed as being placed on equal footing.

One major potential disadvantage of this approach is that many might view it as seriously undervaluing cures that help reduce healthcare costs. By extension, concerns would be raised that this approach would reduce incentives for innovators to tackle the most expensive conditions, cures for which would generate substantial "opportunity gains" freeing up resources to provide better care and access for many others.

The third major alternative for modifying the way that CEA is used to suggest value-based prices for potential cures is some form of "shared savings." This term came into common use in the United States many years ago as a contractual approach between insurers and healthcare providers that would split in some preordained proportion any savings achieved from improved

Table 1. Calculation of value-based prices using different approaches for a new cure of a fatal disease of a 5-year-old child who would die in 10 years with standard therapy. All figures are presented non-discounted

	Annual cost of current treatment	QALYs gained	QALY gain price component	Cost-offset price component	Cumulative "value-based" price
Standard CEA using ICER of $100 000/QALY	$200 000	50	$5 million	$2 million	$7 million
"Repricing" cost offsets at $100 000/QALY threshold	$200 000	50	$5 million	$1 million	$6 million
QALY-based price cap at $100 000/QALY	$200 000	50	$5 million	$0	$5 million
Shared savings 50% for health system	$200 000	50	$5 million	$1 million	$6 million
Shared savings 75% for health system	$200 000	50	$5 million	$500 000	$5.5 million

CEA indicates cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QALY gain price component, Component of price for a cure arising from the QALY gain multiplied by the assumed willingness to pay threshold of $100 000 per QALY; Cost-offset price component, Component of price for a cure arising from the elimination of the costs of best usual care over the years following cure.

Table 2. Calculation of value-based prices using different approaches for a new cure of a nonfatal disabling disease of a 15-year-old person who gains 0.2 QALYs per year in improved quality of life over the ensuing 50 years. All figures are presented non-discounted

	Annual cost of current treatment	QALYs gained	QALY gain price component	Cost-offset price component	Cumulative "value-based" price
Standard CEA using ICER of $100 000/QALY	$200 000	10	$1 million	$10 million	$11 million
"Repricing" cost offsets at $100 000/QALY threshold	$200 000	10	$1 million	$5 million	$6 million
QALY-based price cap at $100 000/QALY	$200 000	10	$1 million	$0	$1 million
Shared savings 50% for health system	$200 000	10	$1 million	$5 million	$6 million
Shared savings 75% for health system	$200 000	10	$1 million	$2.5 million	$3.5 million

CEA indicates cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QALY gain price component, Component of price for a cure arising from the QALY gain multiplied by the assumed willingness to pay threshold of $100 000 per QALY; Cost-offset price component, Component of price for a cure arising from the elimination of the costs of best usual care over the years following cure.

efficiencies in care. When applied to value-based pricing for potential cures, the basic premise would be that innovators should not reap all of the financial rewards related to cost offsets generated by a cure. Instead, those cost-offset "savings" would be shared between innovators and the health system.

Once one begins to contemplate this approach it is clear that the key question is how to determine what percentage of estimated savings should go to the innovator and to the health system. Tables 1 and 2 provide just two proposed ways to split the savings: 50% each or 25% for the innovator and 75% for the health system. As can be seen, either proportional sharing approach produces value-based price estimates that fall in between those calculated using standard CEA methods and the lower "QALY-cap" price.

A "shared savings" value-based price approach could be applied as a single proportion for all potential cures or as a sliding scale dependent on various criteria. Criteria that might help determine whether innovators get a relatively larger or smaller proportion of cost-offset savings could include the following: (1) the magnitude of governmental investment in the basic science underlying the cure has been substantial; (2) the innovator's own research and development costs; (3) whether the cure will potentially eradicate a disease, thus limiting future returns on investment (eg, a cure for HIV), or whether there will always be a recurring incident population born with the condition; and (4) the potential budget impact based on the size of the patient population.

A "shared savings" approach to value-based pricing of a potential cure would have the merit of retaining full valuation for the QALY benefits of a therapy, no matter how large. And this approach would retain, but moderate, greater incentives for innovators to invest in cures for costly conditions. If developed as a sliding scale, it might also allow for the integration of considerations about fair pricing that are widely held by many policymakers.[17–19] As with any CEA-based approaches, however, some stakeholders might continue to believe that the prices suggested by a shared-savings approach are too generous and would not help the health system maintain short-term affordability.

Discussion

It is of course greatly heartening that we should have to face the "dilemma" of figuring out how to manage the pricing and payment for curative therapies. But health systems, insurers, patient groups, clinicians, and innovators are all poorly prepared to think through how best to price and pay for these therapies. When affordability concerns clash with considerations of value, conflict

ensues and access for patients is frequently a casualty. Uncertainty about pricing and payment also complicate efforts to raise funds for investment in the development of new treatments, potentially casting a pall over future efforts to develop new cures.

This article has tried to chart a way forward by identifying the major methodological challenges in employing CEA to suggest value-based price levels for potential cures. Among these challenges we have emphasized one in particular—the challenge presented by the way that standard CEA translates very substantial lifetime health gains and cost offsets into recommended value-based prices. We believe that a new paradigm is needed for CEA results to remain relevant. Our early comparison of possible alternative approaches leads us to favor consideration of some form of "shared savings" approach. Its flexibility and ability to provide a sliding scale of results for consideration by policy makers stands out. But it also will force an important yet difficult public dialog around what proportion of cost savings should flow back to innovators under varying circumstances. This issue is not unique to potential cures and touches on deeply held views, but efforts to address it explicitly are needed.

No matter what methods are sought for new CEA-based approaches to value-based pricing of cures, it is still quite possible that CEA will be rejected by policymakers as being too disconnected from the realities of perceived imperatives such as short-term budgets and profit targets. The major alternative would likely be some kind of pricing linked more to budget impact and "reasonable" profit margins. As Newtonian mechanics today remain fit-for-purpose only for physics at certain scales of size, it may be that CEA cannot be modified enough to fit the needs of policymakers grappling with the enormous scale of health benefits and cost offsets offered by cures. Nonetheless, we believe that the benefits of a long-term perspective on value and considerations of pricing should remain at the heart of the methods of valuing a cure. With the growing tide of cures on the horizon, the time is short for methods and policy development to chart the way forward.

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