

Properly Valuing Gene Replacement Therapy

These revolutionary drugs are expensive, but they offer cures to difficult and costly lifetime conditions.

❖ BY IKE BRANNON AND TONY LOSASSO

Many American say that high drug prices are their biggest concern about health care. It is easy to see why. New drugs often come onto the market at eye-popping prices that few people could afford if they had to pay out of pocket. But few people find themselves paying those prices; rather, their health insurers or the government covers most of the cost. However, there is growing concern that government or insurers will balk at the prices of some of these new drugs.

As novel, transformative drugs and treatments come to market, it is critical to understand the opportunity costs of forgoing such drugs compared to the high list prices the treatments may have. The value of breakthrough treatments on the broader health care system, including private and public payers, downstream health care use, and others, as well as the benefit on overall patient well-being, should be weighed against the drugs' prices when evaluating potential coverage and utilization.

Some of the more expensive treatments hitting the market today are gene and cell therapies. Gene therapy aims to repair, replace, or simply deactivate "dysfunctional" genes in order to restore or establish normal functions. In this way, these drugs attempt to address the underlying cause of a disease rather than just treat the symptoms. Gene therapies can often present a cure for a fatal or debilitating disease, frequently with a one-time treatment. Around 4,000 diseases have been linked to genetic disorders, and gene therapies could potentially save or improve millions of lives. Compared to traditional pharmaceuticals that must be taken frequently over the course of a lifetime, gene therapies represent a truly transformative solution.

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In-the-body gene therapies, which inject a therapeutic gene directly into the bloodstream, as well as out-of-the-body gene therapies, which involve extraction and separation of cells from blood or bone marrow, are both fundamentally different from traditional "small molecule" pharmaceutical treatments. Each has been shown to dramatically and positively affect patients with certain rare and hard-to-treat illnesses such as sickle cell disease, hemophilia, childhood acute lymphoblastic leukemia, and spinal muscular atrophy.

Forgoing a potential disease-curing therapy entails maintaining the existing treatment for a chronic illness or else a hastened death. Besides the patients' continued pain and suffering, the status quo protocol imposes a significant cost on the health care system as well as the broader economy. In the context of those costs, gene therapy and other novel therapies can be seen not only as cost-effective treatments, but also as harbingers for potentially enormous improvements in human health and well-being.

PROPERLY ACCOUNTING FOR THE VALUE OF A LIFE SAVED

To determine the value of any health or safety intervention, we need to estimate a dollar value for each life that is saved, prolonged, or improved. This is a devilishly hard and complicated task: while we might presume that someone whose life hangs in the balance would place a near-infinite value on that life, society cannot afford to do so.

It is paramount to distinguish between the "value of a statistical life" (VSL) and the amount we might devote to saving an individual or a family in perilous, life-threatening circumstance. (See "What Is a Life Worth?" Winter 2004–2005.) The VSL is useful for public policy discussions where we do need to make tradeoffs; in a world of scarcity, we cannot do everything. Spending \$10 trillion on a program that will save just one life is clearly not a wise use of limited resources.



Another reason why public policy should not, as a rule, view life as infinitely valuable is that people do not behave in a manner that suggests they consider their own lives as infinitely valuable. There is a robust literature in the economics of risk that examines human behavior to determine how much people implicitly value their lives as reflected by the everyday choices they make. For instance, occupations that involve cutting down trees or mining coal have a greater probability of injury or death than telemarketing. We can look at the broad difference in compensation between various professions with different degrees of risk, control for other variables that affect compensation, and posit that at least a portion of the difference that remains reflects a wage premium necessary to induce people on the margin to work at a riskier job. That figure, in turn, can help us estimate a VSL.

People make other choices that economists believe reveal the implicit value they place on their lives. For instance, before anti-lock brakes were legally mandated on all new automobiles, we could observe people's decisions about acquiring them. These sorts of considerations also apply to safer bicycle helmets, rear-window cameras in automobiles, and various other safety features that can reduce the chance of injury or death from a crash. From such choices, economists can estimate a rough value that people place on avoiding injury or death.

Finally, psychologists and other social scientists have studied and developed ways to express very low probabilities so that people can better comprehend them and make speculative deci-

sions about risk based on that information. For instance, even the most dangerous jobs in the United States have a low probability of accident or death. The timber industry employs approximately 100,000 loggers. In 2010, 70 loggers lost their lives, or 0.07% of the group. Most people have a difficult time conceptualizing that probability without being given some sort of context.

Several researchers have presented such probabilities to groups of people to ask them what sort of financial or other compensation they would need to accept a modest increase in what is already a very small risk of death.

Federal agencies that regulate consumer safety, transportation, the environment, or the workplace need to incorporate some value of a life saved in benefit-cost analyses of proposed regulations because the justification for most of them is a reduction in injury or death. Given that their incentive, from a public-choice perspective, would be to increase safety regulations and reduce deaths regardless of the attendant costs, we would expect that they will endeavor to use a higher value for a life saved. On the other hand, because Medicare and Medicaid play such a large role in the market, the government has a different perspective with regards to regulatory oversight in health care.

Health care does not typically use a VSL in its decisionmaking. One reason for this is that many health interventions fail to cure illnesses but do manage to extend lives; an intervention that postpones death by a couple months would be judged by most people as being worth less than one that buys a patient two more years.

HEALTH & MEDICINE

It also makes sense to consider the quality of a life extended. For example, for people with kidney disease, there is a big difference between a life on dialysis—a thrice-weekly, physically debilitating procedure that makes work and travel difficult—or life after a kidney transplant that restores a great deal of their previous quality of life.

In medicine, we replace the VSL with a metric called a Quality-Adjusted Life-Year (QALY). The value is typically set administratively and not derived from any revealed preference, unlike the VSL, although some aspects of revealed preference insights—such as how people value being in a specific, less-than-perfect health state—may be used to determine the value of a QALY. It primarily represents the perspective of the regulator.

More importantly, QALY and VSL differ regarding the government incentives involved in imposing a value for each. While government tends to favor a high VSL, a higher value for a QALY can constrain government. For instance, Medicare is an entitlement, which means that government must fund whatever the program promises to provide. Policymakers realize that the program's future health care obligations are woefully underfunded, so their incentive is to impose a low QALY threshold in order to reduce treatment use on the grounds of benefit-cost analysis.

This perspective can lead to a penny-wise but pound-foolish short-term perspective. A low QALY value may reduce spending on gene therapy and similar breakthrough innovations, saving money in the short run, but these therapies often promise a complete cure for a disease. That means patients will be able to work, earn money, pay taxes, and eschew the doctors' visits, conventional medicine, and other health care that their chronic illnesses would entail.

While these innovative cures may seem expensive in the short-run, the long-run benefits they engender can easily make them cost-effective if we properly approach the intervention from a long-run perspective. The problem is, especially on the federal level, policymakers are preoccupied with short-term budget exigencies.

THE TRUE OPPORTUNITY COST OF NOT DOING GENE THERAPY

The cost of a course of treatment for a gene therapy regime alone overstates the incremental cost of the treatment to the health care provider. If the provider rejects the therapy, then the patient must turn to the alternative treatment (if one exists). These treatments are not necessarily more affordable when we properly account for all costs involved.

For instance, the standard treatment for acute lymphoblastic leukemia costs an average of \$40,000 for the first year alone. While the standard regime has come to be remarkably successful, with a five-year survival rate at 68%, those afflicted with the disease who do survive must continue to receive treatment and follow-up care for years. And those for whom the initial treatment fails will receive different treatments and invariably need to undergo future hospitalizations and all that entails.

A potential gene therapy treatment for hemophilia has a

similar calculus. The average annual medical cost associated with treating someone with the disease, which involves the regular use of one of a number of different drugs, currently averages \$270,000. A one-time treatment for hemophilia that obviates the need for such regular pharmaceutical use would likely reduce overall health care expenditures for the illness even at a seven-figure price tag. And this comparison does not consider the substantial costs borne directly by the patients, who must endure the pain and hassle of doctor visits, hospital readmissions, lost days at work, and general pain and suffering.

It is not just the patients who benefit from these advances; taxpayers also stand to gain from potentially curative treatments. Government, through both Medicare and Medicaid, bears most of the cost of treating chronic illnesses via higher hospital admissions and other indirect treatment costs. Employers and patients also bear a significant additional burden through missed work days or a premature end to employment altogether, resulting in a concomitant loss of income and, for governments, a second cost in the form of lost tax revenue. In other words, government potentially stands to gain from the development of these therapies if policymakers properly view them from a long-term budgetary perspective.

ICER AND ITS EFFECT ON DECISIONMAKING

The Institute for Clinical and Economic Review (ICER) is a nonprofit research institute founded by the health insurance industry nearly 15 years ago to research the clinical success and cost-effectiveness of medical treatments, tests, and procedures. Its stated goal is to help decisionmakers understand and apply evidence to improve value throughout the health care system. Over the course of its relatively short existence, ICER has become a formidable force in the health care marketplace. Many insurers use its Value Assessment Framework to guide their decisions on which drugs and medical services to pay for, as well as how much to pay. In 2015, ICER launched the Emerging Therapy Assessment and Pricing (ETAP) program to specifically address new pharmaceuticals like gene therapy.

Estimating the value of a therapy or drug's efficacy is never a straightforward exercise. It requires placing some valuation not just on months or years of life saved, but also on an improved quality of life—or the value of an incremental improvement over an existing, less expensive drug. Such measurements are fraught with complications. Promoting and over-relying on analyses conducted by an insurer-created entity may present a conflict of interest and lead insurers to forgo covering treatments that patients need and that are cost-effective from a societal perspective. If an ICER report concludes that a drug, device, or treatment is overpriced, insurers can argue that they should not have to cover it or else should pay much less than the company's posted price. Sharply lower drug prices may seem at first blush to be an unalloyed victory for consumers, but if manufacturers cannot recoup the costs of developing and testing drugs, then we will see less development of innovative cures.

These concerns extend to ICER's ETAP program, which was launched, according to ICER, to address "a major area of conflict in the U.S. health care system: rapidly rising costs for innovative new drugs." It released its first reports in late 2015 to some stiff criticism. For example, Peter Neumann and Joshua Cohen, writing in the *New England Journal of Medicine*, called into question the efficacy of ETAP's approach in its analysis of PCSK9 inhibitor drug prices, which it recommended reducing from over \$14,000 to \$2,177 per year. These drugs effectively treat individuals with high cholesterol, including high-risk patients who have not responded well to other treatments. Following the ETAP report, prescriptions for these medicines were frequently rejected. The authors argued that ICER employed an overly rigid approach that goes well beyond mere benefit-cost analysis and injects arbitrary policy goals and metrics into decisionmaking.

Similar concerns have been raised with regard to ICER's approach to evaluating new gene therapies. In January 2018, ICER announced that Spark Therapeutic's groundbreaking one-time gene therapy for a rare form of blindness was priced far too high. It has proactively evaluated the cost-effectiveness of Novartis's soon-to-be-approved spinal muscular atrophy gene therapy Zolgensma using a similar model, declaring an "appropriate" price of \$2 million per treatment.

A common complaint is that ICER's evaluation system is overly rigid and imposes a "one size fits all" framework on complex drug-pricing decisions. A recent report by the policy-analysis group Xcenda noted that ICER's recommendations could significantly limit patient access to a wide variety of therapies for Medicare Part B beneficiaries. It seems likely that the same would be true for the broader population.

While ICER does not have authority over reimbursement decisions, the credibility afforded by its ostensibly independent status has led payers and pharmacy benefit managers to use its analyses to establish coverage criteria, determine formulary placement, and negotiate discounts from drug manufacturers.

Rather than over-relying on ICER assessments, policymakers should view these as just one additional data point. To maximize the full cost-savings benefits of gene and cell therapies, policymakers and payers alike must consider a wider set of criteria, including societal costs that can be eliminated—for the first time—by disease cures.

THE PATH FORWARD

Wharton School economist Mark Pauly has argued that individuals should be able to choose health plans with different QALY thresholds for coverage of treatment options. People with preferences for expansive coverage of all viable options, whatever the cost—say, \$500,000 per QALY saved—would have all such services covered. And they would pay a higher premium for their health insurance. Conversely, people with preferences consistent with a \$100,000 per QALY saved threshold would obtain coverage at a lower premium.

Ex post regret could become an issue with such insurance policies, although this is in principle no different from someone who chooses to forgo collision coverage in automobile insurance only to wreck his car. Regret abounds in such a scenario. Nevertheless, coverage of costlier treatments could be available for the regretful consumer, perhaps with cost-sharing.

The clear role of public policy here is to ensure high-quality studies to arrive at meaningful and understandable QALY values, and to make certain that consumers are able to understand the tradeoffs involved between different coverage options. The virtue of allowing consumer choice is that a one-size, top-down approach that uses a semi-transparent algorithm to decide what should be covered and at what price does not fit everyone. The risk averse, those in poor health, or individuals who simply value options may see things differently than enlightened and—indeed—well-intentioned bureaucrats.

The point is that transparent market signals will be sent to consumers in the form of health insurance premiums and those signals will induce enrollment behavior. It works now for deductible levels and other forms of cost-sharing: higher cost-sharing results in lower premiums, and consumers choose in accordance with their preferences. Importantly, a willingness to enroll in high-QALY plans will serve as a pricing signal to innovative manufacturers. In other words, the explicit consequences of higher prices would be manifested in the form of fewer potential consumers.

In short, it is just what the health care sector needs: more market forces and less government coercion.

PROPERLY ACCOUNTING FOR HEALTH CARE GAINS

The list prices for today's cutting-edge gene therapy treatments invariably elicit outrage. The customary response to this outcry has been to point out the very high costs of researching and developing such therapies, which can easily exceed \$1 billion after testing for safety and efficacy. Without high margins, these drugs may never be created to begin with.

We suggest that we take care to consider the health care costs that would be incurred in the absence of such treatments, which have the potential to cure chronic or potentially deadly diseases. We submit that if we properly quantify the value of a life saved, as well as consider the potential treatment costs throughout our health care system that would be necessary otherwise, many of these therapies should be properly viewed as cost-effective interventions even without considering the substantial price discounts typically given to insurance companies and other providers. Any honest discussion of the cost of gene therapy or other blockbuster discoveries should acknowledge this reality. R

READINGS

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- "Measuring the Value of Prescription Drugs," by Peter J. Neumann and Joshua T. Cohen. *New England Journal of Medicine* 373: 2595–2597 (2015).