The special case of gene therapy pricing

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Gene therapy companies that pursue high, one-time payments for their products risk a backlash from payors. A better solution may lie in a pay-for-performance model.

After three decades of research, gene therapy is showing success in the clinic with an emphasis on rare, inherited disorders[1]. However, the scientific breakthroughs that established the technical foundation of the field—long-term engraftment of the curative gene after a single administration—have created several novel business challenges. Addressing these challenges effectively will be critical to realizing the transformative potential of this powerful technology.

Most fundamentally, the healthcare system will soon face the challenge of how to encourage appropriate investment for potentially lifesaving therapies for relatively rare diseases that involve only a single treatment. Unlike rare disease treatments that are regularly administered over decades, gene therapy would, under current models, be administered only once, providing many years, if not a lifetime, of biological activity and clinical benefit. Under current reimbursement systems, this therapy would be paid once at the time it is administered. To encourage investment in the development of these therapies, payments in excess of $1 million may be needed. We suggest an alternative approach to a high, single payment, whereby value is captured through annuity payments received over a specified period based on evidence that the treatment continues to be effective.

The emergence of gene therapies

These financing and underwriting issues are now pressing, as gene therapy has advanced rapidly over the past decade. The first models of gene therapy that emerged in the 1980s were based on *ex vivo* approaches, where the patient's autologous cells were genetically modified *ex vivo* before transplantation[2]. This approach was shown to be successful in diseases, such as severe combined immune deficiency, in which the bone marrow stem cell was the target of the genetic modification, using vectors based on retroviruses. A potentially more versatile approach is to directly deliver the gene to the patient by *in vivo* gene therapy. For this to work, the vector has to seek out the desired target cells *in vivo* following injection and deliver the gene into the nucleus. This Commentary focuses on pricing strategies for *in vivo* gene therapy, although similar strategies could be considered in the commercialization of *ex vivo* gene therapy.

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Payers may balk at the prices of 'one-and-done' gene therapies if they have to pay upfront.

Vectors based on a family of viruses called adeno-associated viruses (AAV) emerged over the past 20 years as a preferred platform for *in vivo* gene therapy[3]. Using these viruses, researchers demonstrated that genes could be inserted into a variety of target cells, tissues and organs, including liver, muscle, retina and the central nervous system. Studies in large animal models of human diseases paved the way for clinical trials that revealed, for example, improvement of visual function in patients with a rare form of congenital blindness[4] and partial reversal of clotting defects in patients with hemophilia B[5]. Ongoing clinical and preclinical studies in these diseases have demonstrated stable gene engraftment, and in some cases ongoing clinical benefit, for as long as ten years after a single injection of vector[6].

A critical milestone was achieved in 2012 when the company UniQure (Amsterdam, the Netherlands) received market authorization from the European Medicines Agency of an AAV-based product called Glybera (alipogene

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tiparvovec) that corrected a deficiency of lipoprotein lipase in patients with a severe form of hypertriglyceridemia[7]. This represented the first, and to date only, approved gene therapy product in the West. Launch of the product in Europe is on hold, pending the successful negotiation of the list price for the one-time treatment[8]. A process for seeking FDA approval of Glybera in the United States has been initiated.

Rare diseases as potential commercial markets

Rare diseases were long considered poor candidates for research under any business model, in that there had appeared to be insufficient patient populations to generate what a pharmaceutical firm might consider an appropriate return on investment. As a result, 'orphan diseases' were long ignored, even after the development of 'orphan drugs' became more feasible with the advent of new therapeutic technologies. This began to change with passage of the Orphan Drug Act of 1983 in the United States, which provided pharmaceutical manufacturers with grants, tax credits and a period of market exclusivity for compounds that could treat rare diseases[9].

Once a few pioneering companies made the investments required to successfully develop the first orphan drugs, it soon became clear that insurance companies were prepared to reimburse the comparatively high prices for such drugs, especially when prodded by advocates for specific diseases, demonstrating that orphan drugs could in fact provide an attractive business model for biopharmaceutical manufacturers[10]. In essentially all of these cases, value was realized through repeated administration of the medication over the life of the patient. Thus, even though the target population is generally small for orphan drugs, high prices and regular administration of repeated doses could make a business case. The contrast with gene therapy, especially therapy that produces a durable cure with one administration, is clear.

Policy considerations on pricing

Recent policy discussions about vaccine development may shed some further light on pricing alternatives. Like gene therapy, many vaccines are often 'one and done', preventing morbidity and mortality long after injection. However, the most prevalent vaccine, the influenza vaccine, is given annually, and many other common bacterial diseases must be given periodically. We have recently entered what some call the golden era of vaccine development, with many new products coming on the market. But the cost is rising rapidly. In turn, US policymakers have asked if the government, through the Vaccines for Children program, should exert a moderating influence on prices, given its role as the major purchaser. Manufacturers object, pointing out that sufficient return must be gained to finance the research needed to prolong this golden age. The same dynamic is likely to play out, only with much bigger stakes, in gene therapy[11,12].

A real world example helps suggest the outline of the pricing issues. Hemophilia B affects about 1 in 20,000 males[13]. Therapy consists of treatment of bleeding episodes with replacement factors such as recombinant factor IX, which carries an average price that translates into $200,000–300,000 per year, or $4–6 million in therapy costs (given 30–40 years of treatment and discounting for inflation). An *in vivo* gene therapy approach for hemophilia B is currently in advanced development[5]. If this therapy essentially creates a lifetime cure, then the accumulated costs of chronic protein replacement are averted. One would presume that gene therapy will have to represent a savings over replacement factors for insurers to approve its use, although this could be accomplished with a price for the one-time treatment that is still in excess of $1 million.

Gene therapy reimbursement considerations

Although a large one-time payment for gene therapy may be the simplest approach, it is fraught with substantial practical and policy risks. Approval of gene therapy products will necessarily be based on data derived from trials captured over a period of time substantially shorter than the expected duration of the therapy. Payers may be reluctant to structure a one-time payment over a 'projected' duration of efficacy. In addition, the rollout of a novel treatment with a price tag of greater than $1 million will likely be criticized in the current environment of reducing healthcare costs. These criticisms may emerge, despite the fact that truly effective gene therapy treatments may reduce the overall financial burden to the healthcare system. As a result, gene therapy breakthroughs may face substantial obstacles if reimbursement is not thoughtfully structured.

An example of concerns over drug pricing is the recently approved Gilead drug, Sovaldi (sofosbuvir), which demonstrates impressive efficacy against hepatitis C. The $84,000 price of the two-month treatment sparked the ire of the US Congress, whose members wrote letters and convened hearings about it being excessive and beyond the reach of many afflicted with the disease. Lost in the discussion was the fact that Sovaldi was not priced higher than its less effective alternatives, and that it represented a cure of a prevalent infectious disease[14]. Against this background, gene therapy breakthroughs might face real opposition in the US healthcare system if not priced carefully.

Some might argue that many conventional therapies are very expensive already and are accommodated by the health insurance system in the United States. A liver transplant, for example, can cost up to $300,000, far more if complications occur. But gene therapy is not directly comparable for at least two reasons. First, physicians and hospitals that transplant livers know they will be compensated at market rates through existing contracts—gene developers lack that assurance. And second, end-stage liver disease should occur randomly and rather unpredictably in a population of patients, whereas the set of patients with gene disorders are well identified. Thus, the lack of predictability for investors and the difficulty of administering insurance for genetic disorders is what creates the difference with therapies already in routine clinical practice.

Addressing the market failure directly is therefore critical to finding solutions. In addition, we need to understand what role the government would play. There is precedent for an annuity-based model for reimbursement. In fact, many policy makers and payers have long advocated that new drugs be reimbursed based on real world results, a so-called pay-for-performance basis. Both in Europe and the United States, insurers and pharmaceutical manufacturers have experimented with pay-for-performance reimbursement in which the compensation is based on certain outcome measures[15]. This approach may be simplest to implement when there is a single payer, such as the National Health System in the United Kingdom. Nonetheless, one could consider a periodic payment for a one-time therapy in any payer context. For example, in the case of protein replacement for hemophilia B, an annual payment of $150,000 per year, so long as gene therapy 'works' would be less than the cost of alternative lifetime therapies for the healthcare system. This would seem to be preferable to a single payment, which, given the assumptions above, would require a one-time payment of $4–6 million to be comparatively priced to existing therapies. From an investor viewpoint, solving the reimbursement dilemma would eliminate the otherwise perverse incentive to prioritize an investment in a repeatedly administered drug, with all its attendant costs to patients, families and the health system, to a one-time therapy for the same disease.

Historically, this kind of approach would not have worked in the United States, where insurance coverage for individuals has typically changed in a relatively hectic fashion (on average, every two to three years), and insurers were allowed to avoid 'bad risk'

patients. But under the new set of rules put in place by the Patient Protection and Affordable Care Act, the context may exist for such a pay-as-you-go model. If gene therapy is the standard of care, then qualified plans may be required to offer it as part of the minimum essential benefits package. As well, plans can no longer limit lifetime benefits, nor discriminate based on disease[16]. So the context for annuity-style payment in a continuous insured relationship exists today in the United States in a way it did not before healthcare reform.

A patient could thus theoretically undergo gene therapy, and the payment from the insurer could be an annual fee, so long as the therapy worked. This payment could continue as long as the treatment continued to work, up to a limit established at the time of administration that would be commensurate with a discount off the price of an existing therapy. The original annuity payment could also be set with certain types of 're-opener' clauses, such as with patent expiration, or if a less expensive new therapy came on line—thus subjecting the gene therapy annuity to the same vagaries of market competition that standard pharmaceuticals face. If that insurer withdrew its policy, another qualified plan would have to accept the patient and—to make a system like the one outlined here work—also accept the annuity fee.

In some ways, the critical issue will be the calculation of the original price, one that other successor insurers would presumably have to honor. This might be solved by the government, which, because many of the patients with rare diseases are disabled and thus qualify for Medicare, would have to set a Medicare price. The Medicare precedent could set a reference price for the commercial market, and very small revisions to federal law could guarantee that successor insurers would honor the Medicare pricing set by an original insurer.

Of course, Medicare would want to get as attractive a bargain as possible for the gene therapy, and gene therapy companies and their investors might not be happy with an approach that does not allow them to charge more for their product than the Medicare price. Even so, the alternative may not be attractive—charging 'full freight' for the one-time therapy at the time of therapy, which would be difficult from an actuarial standpoint and could lead to market failure. No one insurer would want to be the first to cover the medication for fear of adverse selection; that is, all the patients with a particular illness seeking policies from the one insurer providing coverage, thereby driving up costs for that insurer. The Affordable Care Act rules do not allow pre-existing condition exclusions. As well, the government should be in a position to weigh averted costs and also take into account the costs of development.

Another key challenge in developing an annuity model along these lines is the link between payments and an ongoing demonstration of efficacy and safety. Clinical efficacy of a typical pharmaceutical product is based on rigorous and large trials as determined by regulatory agencies. This is a very different analysis than the kind of longitudinal assessment of efficacy within individuals that would be required to justify continued payments. In a few cases, this could include a validated surrogate endpoint, such as stable reduction of low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia treated with gene therapy. However, in most diseases, one would need to establish a nonvalidated biomarker that can be easily and precisely measured and would reasonably correlate with efficacy. An example would be plasma measures of clotting in hemophilia patients treated with gene therapy. Performance against these measures would then act as another 're-opener' of the annuity payment.

The annuity system would be attractive to payers in that the companies selling the drugs would participate in true risk sharing, meaning their continued reimbursement is also dependent on some measurement of clinical efficacy. Indeed, the original negotiation could be based not just on biomarker performance, but true clinical outcomes. For example, a treatment like Glybera for high triglycerides that showed a reduction in biomarkers but no reduction in the frequency or cost of hospitalization—acute pancreatitis attacks are the greatest burden of the disease—may not be sufficient for payers. Including such measures in a payment system would require companies developing gene treatments to become closer partners with healthcare providers, using resources such as their patient services teams to monitor behavior beyond drug usage. Clinical trials would likely have to be 'powered' to demonstrate success in outcomes.

A few other critical issues should be considered before implementing a pay-for-performance model. First, this kind of injection therapy would have traditionally been administered through the physician/procedure reimbursement rather than as a drug—so-called Part B as opposed to Part D in the Medicare system. Medicare's decision about how it will pay will be critical in deciding whether the administration falls to health plans (Part B) or pharmacy benefit managers (Part D). Second, hand-off of patients—when one insurer or primary benefit manager succeeds another—will be key, but most administrators have very well-honed systems for ensuring continued coverage of specific medications and therapies.

Conclusions

In summary, gene therapy presents both enormous potential for improving the health of severely afflicted patients, and some real challenges for traditional models of therapy development and reimbursement. The fact that one intervention can provide a cure, replacing long-term costs of treatment, but provide a less attractive return for investors, makes investment in gene therapy a problem that multiple stakeholders need to work together to solve. To attract appropriate capital, gene therapy entrepreneurs need a durable income stream, based on the market value of the product. A pay-for-performance model based on the thoughtful development of efficacy metrics that can be transferred between succeeding insurers seems to present a reasonable and practical solution.

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The authors declare competing financial interests: details are available in the online version of the paper (doi:10.1038/nbt.3003).

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