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PERSPECTIVE

The Daunting Economics of Therapeutic Genome Editing

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Abstract

There is no shortage of enthusiasm for the clinical potential of CRISPR-based genome editing: many life-changing cures appear to be just around the corner. However, as mature genetic therapies reach the market, it seems that million-dollar price tags are the new normal. Several factors contribute to the extreme pricing of next-generation medicines, including the need to recoup development costs, the undeniable value of these powerful therapies, and the inherent technical challenges of manufacture and delivery. CRISPR technology has been hailed as a great leveler and a democratizing force in biomedicine. But for this principle to hold true in clinical contexts, therapeutic genome editing must avoid several pitfalls that could substantially limit access to its transformative potential, especially in the developing world.

Introduction

From experienced genome engineers to members of the news-consuming general public, people are excited about the prospects for CRISPR-based therapies. The technology is still relatively new, however, and the first efforts are just now entering clinical trials. The operative word here is ''technology'': although CRISPR has both simplified and accelerated genetic research, clinical uses still require considerable expertise in design, production, and delivery of the therapeutic materials. Like other high-tech treatments, therapies based on genome editing will have high price tags, inherently resulting in barriers to access. In this Perspective, we explore how this impacts the development and deployment of these life-changing technologies.

Therapeutic genome editing is in its infancy, but a number of promising examples have made their way toward the clinic. The first clinical trial, funded by Sangamo Therapeutics, began in 2009 and involved zinc-finger nucleases (ZFNs) targeting the *CCR5* gene to provide protection against human immunodeficiency virus type 1 (HIV-1).[1] Currently approved trials using the CRISPR platform include enhancements of chimeric antigen receptor (CAR) T-cell efficacy, treatment of sickle cell disease (SCD) and β-thalassemia, and approaches to inherited eye disease. Genome editing also represents an appealing approach to treating neuromuscular disorders, including Duchenne muscular dystrophy.[2] Therapeutic applications that are in or nearing the clinic are listed in Table 1.

For many diseases, genome editing has the potential to be a transformative approach to medicine that has a number of advantageous features compared to other therapeutics. Unlike drug treatments, it addresses the underlying cause of disease at the gene level. Because it delivers a genetic modification, a one-time treatment can provide a lasting therapeutic benefit. Genome editing makes modifications at normal chromosomal loci, so the natural regulatory controls on the target genes are retained. This contrasts with gene-addition approaches (e.g., ''traditional'' gene therapy) that typically integrate therapeutic genes at essentially random locations, in which cases the regulatory elements must be included in the vector in hopes of providing an appropriate level and timing of expression.

Careful consideration of the disease target is important in the development of a novel genetic therapy. In contrast to gene therapy (replacement) strategies that introduce an exogenous gene, genome editing is especially efficient at disrupting the function of a gene. This fact likely motivated the selection of *CCR5* knockout as a strategy for inducing HIV resistance. Interestingly, the complexities of HIV biology and the moderate efficiency of the early incarnation of ZFN technology resulted in a clinical trial

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that did not eliminate infection. A recent report involving CRISPR-mediated *CCR5* knockout in hematopoietic progenitor cells of a single patient recapitulates the findings of the Sangamo study: encouragingly, the procedure was not associated with any adverse events, but control of viremia was not attained.[3]

Sangamo is now focusing on ZFN-mediated strategies to address SCD, a monogenic disease for which a clear path to a cure exists. Because even low levels of functional hemoglobin are expected to provide a clinical benefit, it is reasonable to advance approaches relying on either incorporation of a corrective DNA sequence for β-globin via homologous recombination[4] or disruption strategies capable of reactivating expression of fetal hemoglobin.[5]

Costs of Current Genetic Therapies

While gene editing offers a number of novel and beneficial features, when it comes to practical issues, there is much to be learned from prior advances in genetic medicine. These include traditional gene therapy,[6] which relies on the introduction of a beneficial transgene; engineered cell therapy,[7] which involves transplantation of autologous or allogeneic cells that have been engineered to introduce desired properties; and non-genetic approaches such as short interfering RNAs (siRNAs),[8] antisense oligonucleotides (ASOs),[9] and protein biologics such as engineered antibodies.[10]

These molecular therapies have typically been developed to address rare genetic diseases with substantial unmet clinical need, which establishes an uphill battle from the outset. Although a typical small-molecule drug can recoup the substantial costs of development and clinical testing via repeated sales to a market of thousands or millions of patients, a genetic therapy may only be applicable to a few dozen patients, and a one-time (or annual) high-efficacy administration often supplants the daily pill format. In hopes of offsetting these factors, treatments are sold for amounts as high as $2 million. In addition to the small patient populations and limited doses, other factors driving up prices are the burden associated with the production of viral vectors and the complications inherent in manufacturing delicate engineered cell therapies.

Development of these complex and highly specific therapies has historically been driven, at least in part, by the Orphan Drug Act (ODA)—a 1983 law passed in the United States that provides an economic stimulus for work to address rare and overlooked diseases. Although the tax incentives and protracted patent protection conferred by the ODA have rendered drug development for rare diseases profitable,[11] there are cases of effective genetic therapies that have proven too expensive to reach patients in need.

Glybera, a gene therapy for lipoprotein lipase deficiency employing an adeno-associated virus vector, debuted in Europe in 2012 at a record price of about $1 million.[12] Assessors in France and Germany subsequently found that the clinical benefits failed to offset the associated cost.[13] After being administered to just 31 people (most of whom were part of trials), Glybera was ultimately discontinued, and its final three doses were administered at a cost of just €1 each.[14] This striking example demonstrates that even a safe and effective therapeutic will have limited real-world impact if its cost is too great.

Despite this high-profile case, stratospheric prices for genetic therapies have persisted. Most notably, Novartis recently made headlines for the pricing of Zolgensma—a one-time gene replacement therapy to treat spinal muscular atrophy—at more than $2 million.[15] The company's rationale behind this pricing is twofold. First, their therapy was presented as a cheaper alternative to the lifetime costs associated with Biogen's Spinraza, an ASO therapy ($750,000 for the initial dose and $375,000 for subsequent annual doses, totaling more than $4 million for the first decade of care). Second, organizations responsible for clinical-economic review (e.g., the Institute for Clincial and Economic Revoew in the United States and the National Institute for Health and Care Excellent in the United Kingdom[16]) calculate that a year of greatly improved life can be valued at $100,000, and so decades of such improvement would reasonably justify a $2 million investment.

Although the high prices of these genetic therapies can be justified, this does not diminish the very real economic burden they entail. Not all insurance providers cover these treatments, and there are many living without insurance in the United States. The U.S. tops health-care spending globally according to multiple metrics: a total of $3.5 trillion in 2017, which corresponds to more than $10,000 per person and about 18% of GDP.[17] This massive market may be enabling extravagantly high prices for cutting-edge diseases, since insurers will feel only a minor sting when very small numbers of patients are covered for expensive treatments.

Broadening the Impact of Genetic Medicine

Several examples illustrate situations where more affordable genome-editing therapies could have a substantial impact. More than four million people worldwide have SCD. The vast majority are in the developing world, where access to cell therapy—either a traditional bone-marrow transplant or an autologous transplant of the patient's corrected cells—is essentially unavailable. Even next-generation *in vivo* therapy

Table 1. Clinical trials using genome editing approved by the food and drug administration

Disease	*Mutation/target*	*Intended edit*
HPV-related cervical cancer	HPV infection	HPV inactivation
AIDS	HIV-1 infection	CCR5 inactivation in hHSPCs
Multiple cancers	CAR T cells	KO of endogenous TCR and PD-1
B-cell cancers	CAR T cells	KO of endogenous TCR and B2M
CD19+ leukemia, lymphoma	CAR T cells	KO of endogenous HPK1
β-thalassemia	β-globin gene defect	KO of BCL11A enhancer
Sickle cell disease	β-globin gene defect	KO of BCL11A enhancer
Sickle cell disease	β-globin gene defect	Mutation correction
Leber congenital amaurosis 10	CEP290 intron mutation	KO of intron mutation
Hurler syndrome (MPS I)	α-L-iduronidase mutation	Insertion of IDUA gene
Hunter syndrome (MPS II)	Iduronate-2-sulfatase mutation	Insertion of IDS gene
Hemophilia B	Factor IX mutation	Insertion of factor IX gene

Source: Clinicaltrials.gov. The CAR T-cell entries use gene knockouts to enhance the efficacy of those cells in cancer immunotherapy and are being pursued for several cancers. The last three entries employ ZFNs to catalyze the insertion of a therapeutic gene into the first intron of the serum albumin locus, rather than targeting the defective gene at its natural location.

HPV, human papillomavirus; AIDS, acquired immune deficiency syndrome; MPS, mucopolysaccharidosis; CAR, chimeric antigen receptor; KO, knockout; TALEN, transcription activator-like effective nucleases; ZFN, zinc finger nuclease; hHSPC, human hematopoietic stem/progenitor cell; AAV, adeno-associated virus.

would be just as impractical if it were priced similarly to the examples discussed above.

Reported *ex vivo* genome-editing trials that involved making a *CCR5* knockout in patient cells (either T cells[1] or their hematopoietic progenitors[3]) to combat HIV showed that these procedures could be done safely. In principle, performing highly efficient knockout of one or more essential host receptors in bone marrow–derived stem cells would provide lifelong protection against HIV-1. For such an approach to be more appealing than current antiretroviral therapy, however, the treatment price of a genome editing therapy would have to be competitive, the side effects of the drugs notwithstanding.[18] *Ex vivo* interventions are inherently expensive and present barriers to access. So, *in vivo* administration must be enabled before widespread use of any such strategy can be practically adopted.

Identification of PCSK9 as a target for lowering low-density lipoprotein cholesterol has led multiple groups to target it for disruption with CRISPR. As the protein is active in the liver, it provides a plausible target for *in vivo* delivery, and experiments in animal models have proved at least partially effective.[19,20] Such a treatment would have to compete with the now-ubiquitous and affordable statins. Indeed, repeat-dose biologics (i.e., the antibodies alirocumab and evolocumab) that inhibit PCSK9 have demonstrated efficacy but have proven too expensive to find a market.[21]

While it may be tempting to blame corporate opportunism for the extreme pricing of modern genetic therapies, there are two tangible factors that must be addressed before next-generation medicines can be rendered broadly affordable: (1) simplifying regulatory frameworks for personalized genetic medicines, and (2) streamlining manufacture/delivery.

Simplifying regulatory frameworks

This point looms especially large over the field of therapeutic genome editing in the CRISPR era. Enzymes such as Cas9 are incredibly powerful and versatile because there are extremely low technical barriers to creating a truly personalized therapeutic—one that addresses the precise mutation responsible for a specific patient's condition with a unique guide RNA. As it is now feasible to perform genetic diagnosis based on an individual's genome sequence, it would seem reasonable that bespoke genome-editing therapies would be just around the corner. Frustratingly, even if challenges such as delivery and manufacture are sufficiently addressed (see below), it is possible that current regulatory mechanisms might hinder development.

Clinical trials performed in the United States cost tens of millions of dollars, and current regulatory frameworks do not allow blanket approval of a personalization-compatible platform such as CRISPR editors. This presents a conundrum for widespread adoption of personalized genome-editing therapeutics: how can the costs of a clinical trial be offset if very few patients will be treated with a given therapeutic?

This raises a tangential but important topic: how can personalized therapies be assessed for safety, and will they ever be fit for applications beyond ''compassionate use''? A possible solution is one in which the editing platform and the means by which it is delivered are generally assessed for safety, while the specific edit a given patient needs would be tested only in cells derived from that patient in order to safeguard against unexpected outcomes specific to that particular locus and corresponding effector.

Platform	Delivery	Location	Status
CRISPR, TALEN	Plasmid	Guangdong, China	Unknown
CRISPR, TALEN, ZFN	*Ex vivo*	Various sites	Recruiting
CRISPR	*Ex vivo*	Various sites	Recruiting
CRISPR	*Ex vivo*	Various sites	Recruiting
CRISPR	*Ex vivo*	Shannxi, China	Recruiting
CRISPR, ZFN	*Ex vivo*; hHSPCs	Various sites	Recruiting
CRISPR, ZFN	*Ex vivo*; hHSPCs	Various sites	Recruiting
CRISPR	*Ex vivo*; induced HSCs	Not specified	Not yet recruiting
CRISPR	*In vivo* injection, AAV vector	Various sites	Recruiting
ZFN	*In vivo* injection, AAV vector	Various sites	Active
ZFN	*In vivo* injection, AAV vector	Various sites	Active
ZFN	*In vivo* injection, AAV vector	Various sites	Active

Delivery and manufacture

The other key impediments to affordable (and thus accessible) genome-editing therapies are delivery and manufacture, which go hand in hand. We have noted how the expense of individualized *ex vivo* therapy will likely prohibit broad use. It is tempting to imagine that *in vivo* delivery with viral vectors might be cheaper. However, scale-up of successful approaches for hematopoietic stem cells in small-animal models[22] would require viral infusions estimated to cost up to $1 billion per patient.[23] Editing of other cell types is much more feasible, although a liver-focused lentiviral gene therapy for β-thalassemia[24] nevertheless costs $1.8 million. Indeed, development and utilization of tissue-targeted viral vectors holds great appeal; such technology would reduce required doses and minimize risks of side effects.[25]

The challenges of viral vector manufacture are a major factor in development of affordable genome-editing therapeutics, hence the growing interest in nonviral platforms that are compatible with less demanding production pipelines.[26] Although lipid nanoparticle (LNP) vectored genetic therapies are latecomers to the field, there is encouraging progress in the form of the approval of Patisiran, an siRNA drug for transthyretin-mediated amyloidosis,[27] and Moderna's development of mRNA therapeutics that rely on LNPs for delivery.[28]

Conclusion

Beyond the inherent technical issues associated with potential CRISPR therapies, such as the inefficiency of homologous repair and concerns about off-target mutagenesis, the costs of manufacture, testing, and delivery will have to be sharply reduced in order to make the benefits of genome editing available to those most in need. We exhort genome editors, regulators, and the broader bioengineering community to accept the challenge to make genome editing therapeutics affordable and accessible, which would represent a massive contribution to global health justice.

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