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PERSPECTIVE CRISPR Trials

Affordable Pricing of CRISPR Treatments is a Pressing Ethical Imperative

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Abstract

Casgevy, the world's first approved CRISPR-based cell therapy, has been priced at $2.2 million per patient. Although this hefty price tag was widely anticipated, the extremely high cost of this and other cell and gene therapies poses a major ethical issue in terms of equitable access and global health. In this Perspective, we argue that lowering the prices of future CRISPR therapies is an urgent ethical imperative. Although we focus on Casgevy as a case study, much of our analysis can be extrapolated to the controversies over affordable access to other gene and cell therapies. First, we explain why this first-of-its-kind CRISPR therapy might be so expensive. We then analyze the ethical issues of equity and global health of early CRISPR treatments. Next, we discuss potential solutions to lower the prices of CRISPR gene therapies. We conclude that the approval of CRISPR transforms our obligations of justice and compels us to bring future gene therapies to the maximum possible number of patients with serious genetic diseases at affordable prices.

Introduction

CRISPR is unchained. Since Jennifer Doudna, Emmanuelle Charpentier, and colleagues introduced bacterial CRISPR tools as gene editors in 2012,[1] the science has advanced at a stunning pace to develop a powerful tool for medicine. The first CRISPR-based gene treatment was approved by the U.S. Food and Drug Administration (FDA) on December 8, 2023[2] and the European Medicines Agency (EMA) on 12 February 2024,[3] following approval by the U.K.'s Medicine & Healthcare Products Regulatory Agency on November 16.[4]

Casgevy (exagamglogene autotemcel), developed by Vertex Pharmaceuticals and CRISPR Therapeutics, is now available for patients aged 12 and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched HSC donor is not available, and β-thalassemia patients for HSC transplantation is appropriate and a HLA-matched related HSC donor is not available.[5,6] SCD and β-thalassemia are severe, rare genetic diseases characterized by abnormal production of hemoglobin. Patients with both disorders require regular blood transfusions and suffer lifelong blood abnormalities. SCD is a notoriously painful condition, with many patients enduring frequent VOCs, which can be fatal. Both diseases are associated with mutations within the β-globin gene, one of the two proteins (together with α-globin) constituting adult hemoglobin.

Casgevy is based on a complex *ex vivo* CRISPR therapy. First, blood-producing CD34+ stem cells are extracted from the patient's bone marrow and then modified in the laboratory to edit the *BCL11A* gene, which encodes a repressor that keeps the γ-globin genes inactive in adulthood. The CRISPR editing of the *BCL11A* gene targets its enhancer, thereby reducing its transcription and resulting in much less BCL11A protein being produced. The aim is to reactivate the γ-globin genes in the adult life of the patient to eventually replace the mutant beta-globin gene. Subsequently, the CRISPR-edited blood stem cells are returned to the patient after (s)he receives a busulfan-based myeloablative preconditioning treatment.[7] This procedure has been inspired by pioneering contributions from many investigators, including the lab of Stuart Orkin[8] and has

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been approved after successful clinical trials.[5,6,9] The hemoglobinopathies, SCD, and β-thalassemia have been widely discussed cases to demonstrate the potential of CRISPR for clinical gene therapy.[9,10] This milestone was widely anticipated following the International Summit on Human Genome Editing conference, which was held in London in March 2023. There, Victoria Gray, the first American patient to undergo the procedure in 2019, recounted how CRISPR had changed her life by helping her overcome the ravages of SCD.[11,12] Needless to say, we join the rest of the scientific community in applauding this enormous success.

This medical breakthrough is overshadowed to some extent however by the accompanying price tag. Vertex Pharmaceuticals has set a price of $2.2 million per patient for the U.S. market.[13] Alas, this high price is not surprising. Since their inception in the 1990s, gene and cell therapies have been notoriously expensive treatments. In fact, the priciest medical treatments in the world are gene therapies that are not related to CRISPR.[14,15] Lenmeldy, a gene treatment for a very rare inherited disease called metachromatic leukodystrophy, developed by Orchard Therapeutics, is currently the most expensive drug costing $4.25 million in the United States.[16] Another newly approved gene therapy for SCD, Bluebird's Lyfgenia, has a price tag of $3.1, nearly $1 million more than Casgevy.[17]

Although affordable access is a pervasive challenge regarding emerging gene and cell therapies, our analysis in this perspective is motivated by focusing on Casgevy as a case study. We do so for two reasons. First, CRISPR is a Nobel Prize-winning technology on which many patients with serious genetic diseases have pinned their hopes. Researchers have been fueling this hope over the years and patients may feel disappointed by being unable to access the therapies they have been waiting for. The potential for life-changing cures will be blunted by the million-dollar price tags that are likely to dominate the CRISPR bioeconomy of initial somatic therapies.[18]

Second, the high price of Casgevy raises several ethical and global health issues. Up to 400,000 new cases of SCD appear in the world each year, most of them in Africa.[19] Even if not all are potential candidates due to the stringent clinical eligibility criteria, this high price could become an insurmountable barrier in Europe and elsewhere. If we want the clinical benefits of CRISPR to be maximized and fairly distributed, we must direct joint efforts to make the next gene therapies scalable, fairly priced, and widely affordable. Remarkably, the access limitations to these CRISPR-based therapies are not only scientific or technical—including the clinical eligibility restrictions—but saliently economical.

No doubt, Casgevy shares similar equity problems with other cutting-edge gene and cell therapies. The multimillion-dollar prices of these therapies are often unaffordable for many national health systems, several private insurance plans, and the pockets of most potential recipients. These treatments are therefore incompatible with equitable access. Consequently, many of our reflections below apply not only to Casgevy or other forthcoming CRISPR treatments but also to developments in gene and cell therapy in general.

With this caveat in mind, we structure this perspective as follows. We begin by briefly explaining why Casgevy therapy might be so expensive. We then analyze its main ethical problems in terms of equity and global health. We also identify some of the typical economic problems reported in the literature and discuss some of the proposed solutions. Finally, we reflect that the approval of pioneering CRISPR therapies changes our judgments of fairness, compelling us to bring these innovations to the maximum number of patients afflicted by serious hereditary diseases.

Why It is so Expensive

First-generation CRISPR treatments are expensive for several reasons. Importantly, pharmaceutical companies want to profit from their costly (and potentially risky) investments. This is a legitimate aim. Without these millionaire investments, we would probably not have these clinically beneficial innovations. Often, meeting the regulatory frameworks means that clinical trials cost pharmaceutical companies millions.[18] The fact that these CRISPR cell therapies are intended to involve a single application may also lead pharmaceutical companies to raise their prices. By curing chronic patients, the argument goes, the savings to health systems can be even greater than the price of gene therapy. (However, health systems might distribute these smaller, regular expenditures over many years, whereas, if the gene therapy must be paid at once, this could challenge annual budgets.) Furthermore, only a subset of the potential therapies tested make it to clinical trials, and just a fraction of them eventually pass the safety and efficacy filters. Once a drug is approved, pharmaceutical companies want to compensate for all the previously failed drugs in which they heavily invested.[20] This is also legitimate.

In addition, the clinical success of several gene therapies has triggered the interest of new investors and investment funds, who have now turned their investments from other businesses to medical treatments because they seem economically profitable. These new investors might lack

the patience to wait for revenue streams over a long period. Rather, they want to recover their investments with profits as soon as possible, thereby increasing the prices of these gene therapies further.

Other issues that may well raise the price of these first-of-its-kind CRISPR treatments are their complex manufacture and delivery. The manufacturing requires highly specialized staff, high-tech equipment, and practice-approved quality standards for safety and efficacy reasons.[21] The manufacture of viral vectors, moreover, can be expensive. A cost-effectiveness analysis of a previous *ex vivo* gene therapy for *β*-thalassemia showed that the production of the vectors accounted for as much as 48% of the total cost of treatment.[22] Moreover, the delivery of Casgevy will require a complex health care infrastructure.[7] In particular, the therapy is customized to each and every patient. There is no universal approach as the starting blood stem cells must be derived from the actual patient (autologous bone marrow transplant). The fact that the treatment is *ex vivo* and thus requires editing of the cells in the laboratory by skilled staff also makes the process more expensive.

It has been proposed that *in vivo* treatments—in which the injection of the CRISPR infusion directly modifies the cells—could lower costs.[23] Nevertheless, this is not a magical solution *per se*, as there are *in vivo* gene therapies that match the prices of more expensive *ex vivo* therapies.[18,21] Plus, delivering CRISPR tools *in vivo* might face additional unexpected problems and concerns for the safety of the treatment.

Equity and Global Health Issues: An Ethical Perspective

The EMA has designated Casgevy as an orphan medicine.[3] Typically, the funding of rare diseases, whether for their research or their clinical treatments, tends to be discussed based on economic and noneconomic values. Economic aspects often dominate many initial analyses. For patients, overcoming a chronic and life-threatening disease is priceless.[24] For national health care systems, however, approval of such expensive treatments is usually subject to cost-effectiveness studies and the severity of the disease. In the case of Casgevy, it is crucial to compare the cost of gene therapy with the lifetime costs of continued treatment.[21] If the lifelong health care costs of these patients exceed the cost of the curative treatment, paying for these gene therapies would be economically rational. This calculation should consider that the lower cost of routine treatment is spread out regularly, while the $2.2-million cost of Casgevy could be much more difficult to absorb if it unbalances the annual health care budget.

Beyond economic rationality, in high-income countries with sufficient resources, payment for these treatments could be justified by a number of moral reasons. These include the duty not to abandon people with rare genetic diseases, the duty of rescue, a right-based approach to health, solidarity, and (individual) beneficence reasons.[25] All of these moral arguments would support the funding of such costly treatments, regardless of whether the cost-effectiveness balance is necessarily positive. After all, people with rare genetic diseases have not only been unlucky but arguably may also suffer injustice if they are unfairly impeded to access to existing treatments.

Yet, from a global health perspective, such costly treatments reinforce glaring inequities between countries. Worldwide, >4 million people have SCD, of whom approximately 80% live in sub-Saharan Africa.[26] Due to their high prices, these CRISPR treatments will not reach the countries where this disease is most prevalent and where many patients might be eligible for Casgevy treatment. Indeed, in many sub-Saharan African countries, SCD is not so much a rare disorder but a major public health problem with a large burden of disease. Even worse, in many African countries such as Nigeria, there is still not enough hydroxyurea, an inexpensive drug that significantly improves the quality of SCD patients.[7]

Similarly, other drug candidates such as GBT021601 (Osivelotor), an investigational small-molecule oral drug developed by Pfizer for SCD that is easier to manufacture to large quantities, can have a bigger impact on reducing the global disease burden because of its greater accessibility and scalability.[23] In this light, investments in million-dollar CRISPR therapies entail a remarkable opportunity cost by failing to fund other valuable alternatives that may have more positive impacts on global health. This is problematic on ethical grounds. From a utilitarian perspective, which aims to maximize clinical benefits and minimize the burden of disease for the greatest number of people, expensive treatments such as Casgevy are questionable. According to this view, funds should be used to improve as much health (measured, e.g., by Quality-Adjusted Life-Years) for as many patients as possible, regardless of the country in which they reside.

The market for gene therapies is clearly concentrated in high-income countries.[27] Inequities can also occur within high-resource countries, though. For example, an estimated 100,000 people have SCD in the United States, mostly of African or Central and South American descent, which are populations that already accumulate a

legacy of discrimination and health inequities.[28] The insurance rate of Hispanics (18.0%) and Blacks (10.0%) in the United States is higher than the rate for their white counterparts (6.6%).[29] Furthermore, if we contrast high-income countries from different regions in the world, citizens may also experience significant differences in the opportunity to access gene therapies. The pricing, payment, and reimbursement models for gene therapies are country-dependent and region-specific. Cost-containment measures are often more stringent in Europe than in the United States for gene and cell therapies. For example, the price of the gene therapy Roctavian is $2.9 million in the United States but only $1.5 million in Germany, while the price of Lenmeldy is $4.25 million in the United States but a slightly more reasonable £2.8 million in the United Kingdom.[30] Casgevy's prices in Europe, nevertheless, will depend on negotiations with each member state authority. For now, despite the European Commission's conditional approval of the therapy on 12 February 2024, pricing information in the EU is not publicly available. All in all, the same gene therapy might be more expensive in some countries than in others. This could also be seen as a global health equity issue, as no one can determine whether the region of the world in which they live has more market-oriented or community-oriented health systems, or better cost-containment strategies.

Identifying Problems, Envisioning Solutions

Without a remedy, upfront CRISPR treatments will be an expensive privilege, even for many high-income countries. This is extremely concerning in terms of equity and fair access to health care. To ensure that the therapeutic potential of CRISPR does not remain a false promise, the next developments must be aimed at promoting significantly cheaper therapies. Otherwise, there is a risk of fueling mistrust in science and pharmaceutical innovation. The expected unaffordable prices of gene therapies were, in fact, one of the justifications for controversial self-experimentations with CRISPR, as in the case of HIV-positive Tristan Roberts.[31] In this way, these extraordinary prices can reanimate the biohacker and citizen science communities that defended the democratization of CRISPR against pharmaceuticals. To avoid giving promotion to risky DIY (do-it-yourself) gene therapies, it is worth rethinking the predominant innovation processes along with CRISPR access models.

To begin, waiting for competition among manufacturers to lower prices is an unsatisfactory strategy. Biotechnology initiatives that seek to lower the prices of CRISPR therapies must be supported proactively and with public funds. India is a paradigmatic example in this regard, where the price of one gene therapy has been lowered to ten times less.[32] Also, noteworthy are the clinical trials for *in vivo* treatments for SCD and HIV that seek to create more affordable gene therapies, funded by the Bill & Melinda Gates Foundation and the National Institutes of Health.[11] Decentralizing parts of the process could also make CRISPR therapies cheaper.[21,32] In addition to prioritizing one-and-done therapies, devising easily scalable treatments would be beneficial. Scalability is related to price. Importantly, the multimillion-dollar prices of gene therapies are not always a stable business, since a not negligible percentage of them end up being withdrawn from the market.[16,24] The strategy of setting multimillion-dollar prices is then not necessarily successful for business survival.

Creating gene therapies that are modular and whose elements can be exchanged and equally used for different pathologies might also help to lower the prices for these treatments. This is the pathway explored by Intellia Therapeutics. This company has released gene therapies for two unrelated rare diseases, hereditary transthyretin amyloidosis[33] and hereditary angioedema,[34] which are currently in clinical trials. Both of these gene therapies share the RNA encoding Cas9 and the lipid nanoparticles used for *in vivo* delivery. They differ only in the third component—the specific guide RNA directing Cas9 to the target gene: *TTR* and *KLKB1*, respectively.

The Innovative Genomics Institute (University of California at Berkeley) has also explored some measures worth undertaking to reduce costs and offer gene therapies at more affordable prices.[35] They have produced several interesting findings:

- using a dynamic cost-plus model for pricing new genetic therapies could lead to a sticker price that is a tenth of genetic therapies on the market.
- nonprofit medical research organizations and public benefit corporations offer alternative organizational structures that could in theory reduce the list price. For these to be successful, lower-cost capital (requiring a lower rate of returns) is needed to control costs.
- academic technology transfer offices can play a significant role in improving affordability and access via license provisions and requiring access plans. Lastly, regarding manufacturing, it could be helpful to use various innovations, point-of-care manufacturing, and regulatory streamlining that could lower prices, while maintaining safety and efficacy, as discussed in the latest ARRIGE report.[20]

Nevertheless, it is difficult for these initiatives to come to fruition if there is no coordinated public action

to stimulate them. The COVID-19 pandemic serves as a lesson here. Several countries committed enormous amounts of funding (which had not been previously budgeted) to develop COVID-19 vaccines and distributing them worldwide. Billions of doses were distributed and charged to countries' annual budgets. Therefore, it is possible to mobilize significant funds when there is a will and a need.

Moreover, it is essential to prevent patent wars from delaying the delivery of CRISPR treatments to patients. Litigation over CRISPR intellectual property rights may impede more patients from benefiting from this cutting-edge biotechnology in some countries. The Broad Institute holds the patent to use CRISPR-Cas9 as a human cell editor in the United States, which has been exclusively licensed to Editas Medicine. Vertex agreed to pay Editas $100 million for a nonexclusive license of CRISPR.[36] Interestingly, the CRISPR innovation ecosystem is partly driven by small pharmaceutical companies (such as CRISPR Therapeutics, Beam Therapeutics, Intellia, and Editas) developing a limited number of therapies. Many universities have given exclusivity on CRISPR drugs to start-ups co-founded by their own researchers,[37] often supported by venture capital with a manifest financial interest.[38] Investment funds have provided substantial financing to these companies as the new gold rush and are likely not interested in lowering the prices of the newly approved therapies in order to secure an early return on investment.

Universities and research centers that are supposedly nonprofit should prioritize CRISPR reaching the greatest number of patients,[39] instead of waging patent wars and prioritizing the short-term interests of investment funds. It is worth remembering that these therapies are not solely the fruit of private investment, but generally arise from public–private partnerships, as has been the case with the role of Boston Children's Hospital and the National Institutes of Health in the basic research that helped drive the development of Casgevy.[38] More generally, as Kliegman et al. recently noted, "all approved cell and gene therapies [approved by the FDA] trace their origins to academic or government research institutions."[30] Thus, as CRISPR therapies are also the product of public investment and altruistic donations, their benefits should not be unduly restricted by private interests.

Finally, new treatment schemes are required, such as risk-sharing agreements,[40] where the patient/health system pays a first amount for accessing the therapy, but subsequent payments are dependent on the patient's health and recovery. Alternatives are based on charities and public funds/donations that can be channeled to some hospitals, which could then accept a limited number of patients for treatment. One such initiative involving several hospitals has been launched from the United Kingdom under the name of AGORA.[41]

Conclusions

Gene and cell therapy using CRISPR has to be part of the future of medicine. The >11,000 registered clinical trials on gene therapies (of which around 100 involve CRISPR tools) are a good indication of this aspiration.[42] Nonetheless, it is an ethical imperative that CRISPR treatments and other gene and cell therapies come at a fair price, making efforts to afford them for the maximum number of patients. Otherwise, we would be failing in our obligations to equity and wasting enormous therapeutic potential. There must be a solution that would take into account the legitimate right of pharmaceutical companies to profit from their developments, while putting them into the clinical market at affordable prices, which are payable by the national health systems, public or private, operating in every country.

Finally, the rise of CRISPR therapies transforms our judgments of fairness. Without biotechnologies to remedy it, suffering from a rare genetic condition is arguably bad luck. In a world with CRISPR, however, not being able to treat a serious genetic disease is not a misfortune (an inevitable evil), but an injustice (a preventable evil).[43,44] For CRISPR-based therapies not to reach patients is a double condemnation: that of suffering from a genetic disease and that of not being able to afford the existing treatment to overcome it. We have an ethical duty to make these new treatments not only enough safe and effective but also affordable for as many patients as possible. Eventually, we hope these remarkable therapies will reach all patients, thus fulfilling the fourth principle of bioethics, that of justice. After all, what can be worse than having a child with a rare disease? Having this child, knowing that a cure has been developed and approved, and realizing that the treatment will be unaffordable due to its very expensive price.

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J.R. conceived the main arguments and drafted the initial version of the paper. For the following versions, J.R. and L.M. led the literature review and the rewriting. I.D.M.B.

reviewed subsequent drafts and made substantial contributions to its improvement.

Author Disclosure Statement

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