ARRIGE

Association for Responsible Research and Innovation in Genome Editing

ETHICS OF CRISPR GENE THERAPY

WHITE PAPER

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PREPARED BY:
ARRIGE SCIENTIFIC COMMITTEE

DEMOCRATIZATION OF SCIENCE

Historians of genome editing-based therapies will mark 2023 as the beginning of a new era; one in which previously incurable diseases could be treated with one-and-done therapies that save patients from debilitating pain and a shortened expected lifespan, achievements that build upon earlier 21st century successes with other forms of gene therapy. But we do not yet know which year these historians will mark as the beginning of a new era of generally affordable and equitable gene therapies. We do not even know yet whether such a year will ever arrive. For it to do so, some changes must be made in the ways in which we develop and deliver these therapies.

The first approved gene-editing treatment – Casgevy – was developed by two companies, Vertex Pharmaceuticals and CRISPR Therapeutics, as a treatment for sickle cell disease (SCD). Healthy red blood cells are round and move through small blood vessels to carry oxygen to all parts of the body. In SCD, the red blood cells are deformed, and look like a “sickle.” They can get stuck in the blood vessels, clogging blood flow and causing severe pain as well as a number of complications, including earlier death. Casgevy involves a complicated, difficult and expensive protocol by which a patient’s cells are removed from the body, genetically edited to produce high levels of fetal hemoglobin – which is normally deactivated after birth – and then returned to the body, with the result that debilitating pain is relieved. To do this, patients must undergo many of the grueling steps required for a bone marrow transplant, including extensive hospitalization and a chemotherapy regime that can render the patient infertile, and cause pain and weakness for months. The first patient to be cured of SCD with this regime, Victoria Gray, gave a heart-wrenching description of both the disease and the cure when she gave a keynote address to the Third International Summit on Human Genome Editing in London:

> For 10 minutes, Gray repeatedly choked back tears as she described her life with sickle cell…. She detailed one especially tortuous pain crisis. "During this hospital stay, with a ketamine infusion in one arm and a Dilaudid infusion in the next — but still no pain relief — I called all the doctors into the room and told them I could no longer live like this," …. Gray explained how she finally received the CRISPR gene-edited cells — "supercells," she calls them — as part of a study. "The life that I once felt like I was only existing in, I am now thriving in," …. I stand here before you today as proof that miracles still happen — and that God and science can coexist." As Gray walked off the stage, the crowd gave her a standing ovation [1].

There are dozens of gene-editing therapies in development, and other gene therapies have already been approved. What they have in common is the prospect of a single intervention with lifetime benefits, either to alleviate some symptoms or to actually cure a disease. For early-onset disorders in particular, the savings are vast, both in human terms (pain, suffering, lost opportunities for work and social life) and economic terms (medical costs accrued year after year). However, the incredibly high upfront costs are an enormous obstacle. Vertex announced that the initial price for Casgevy would be over US$2 million, and Bluebird Bio, which also had a gene therapy approach for sickle cell approved, announced an initial price over US$3 million.

[1] Rob Stein, “Sickle cell patient's success with gene editing raises hopes and questions” March 16, 2023

Parents are reporting regular obstacles to private insurance coverage for the gene therapy that is currently approved for young boys with Duchenne muscular dystrophy [2]. In countries with private insurance systems, people often switch insurers over the years. This makes it hard for an insurer to be confident that any lifetime savings will accrue to the same company that paid for the therapy. In addition, prices like these put pressure on sponsors to prove beyond doubt that the therapies will indeed achieve long-term effectiveness. Even in countries with national systems, in which lifetime savings would accrue to the same entity that paid for the costly therapy, there is a high evidentiary standard applied to prove long-term effectiveness. This is the point at which a new form of gene therapy for hemophilia stumbled when reviewed by the UK's cost-effectiveness watchdog, the National Institute for Health and Care Excellence (NICE)[3].

The business model leads to high prices because it is premised on incentivizing R&D investment in innovative new therapies with the promise of near-monopoly market status for a period of time if a therapy proves successful and is approved for sale. Huge sums go into the preclinical and clinical testing of new therapies, many if not most of which will fail. Profits on the therapies that succeed offset those losses. In the case of conventional drugs for chronic conditions, the prices may be set at manageable levels, in the expectation that patients will keep needing (and therefore keep buying) the drugs for months or even years. But a one-time intervention that cures a disease offers only one sale per patient in which to recoup all of the investment for the successful therapy, as well as the failures: an outcome that results in enormously high prices.

The problem is made even more intractable when dealing with rare diseases, as there are so few patients with the condition that the regulatory pathway itself becomes more difficult: more difficult to recruit patients, who may be scattered among many countries; more difficult to manage multiple sites across multiple jurisdictions with different rules governing trials; more difficult to meet the statistical standards that were designed for trials with larger numbers of patients; and more difficult to meet the manufacturing standards that were set for situations in which much larger quantities were being made.

Thus, there are two intersecting problems. For common diseases, the upfront cost of one-and-done treatments for a large number of patients is overwhelming, for both private and public insurers. For rare diseases, the business model and the regulatory system both conspire to make investment unattractive.

Affordability is a key element in making gene therapies accessible to a broader population. To that end, many observers have suggested new business models and new public–private partnerships that would de-risk the R&D investment phase in exchange for moderating price points after approval. Others have suggested amortizing the costs, creating pay-for-performance schemes, or having public insurers create guaranteed markets that could drive down prices [4].

[2] https://mdaquest.org/insurance-denials-for-gene-therapy-treatment-delay-access-to-care/

[3] https://www.fiercepharma.com/pharma/uks-nice-initially-rejects-csl-behrings-pricey-gene-therapy-hemgenix

[4] https://drive.google.com/file/d/1iKWgmNVRtQY41NbAgDhCqdw5sCHFpVms/view

In its influential report on the subject, the Innovative Genomics Institute made the following key findings and suggestions:

Pricing: Use a dynamic cost-plus model for pricing new genetic therapies that could lead to a sticker price that is 10x less than genetic therapies on the market.

Organization and Funding Models: Non-profit medical research organizations and public benefit corporations (B-corps) offer alternative organizational structures that could, in theory, reduce the sticker price. For these to be successful lower-cost capital (requiring a lower rate of returns) is needed to control costs.

Intellectual property: Academic technology transfer offices (TTOs) can play a significant role in improving affordability and access via licenses provisions and requiring access plans.

Manufacturing: Use various innovations, point-of-care manufacturing and regulatory streamlining that could lower prices while maintaining safety and efficacy [5].

However, it took The Innovative Genomics Institute one year of discussions to come up with the above plan, whose goal is to reduce gene therapy costs about 10 times, bringing them from around $2.5 million to $250,000. This is something that could be accepted by health insurers in richer countries, but still does not solve the problem of universal or at least wider availability in other countries .

Although the current costs to healthcare providers of genome-editing therapies are extremely high, there are interesting initiatives related to standardization of production, delivery and regulatory processes that aim to decrease the costs significantly and make such therapies much more accessible to most people in some parts of the world. In the future, they are likely to become available to, and cure, an increasing number of people, eventually reaching those with less insurance coverage in rich societies, thus reversing some aspects of the current inequalities.

Some of these initiatives involve vector-free approaches, but even no vectors are used, which would lower the cost of gene therapy, whatever method is used would have to go through the appropriate processes of regulatory acceptance. Some publications describe the use of various approaches but none of these therapies have been approved so far. Other treatment modalities are available, one of which uses RNA interference to prevent the expression of a disease-causing gene or to change the expression of an inactive gene (Patisiran for hereditary transthyretin-mediated amyloidosis and Nursinersen for Spinal Muscular Atrophy, respectively, with annual costs of about $500,000 and $375,000 per year). Targeted drugs also exist, such as Trikafta for the treatment of cystic fibrosis, but again the cost of this is $300,000 per year. The difference between these drugs and gene therapy is obvious – gene therapy is given once, whereas the drugs for genetic diseases must be taken over a lifetime.

[5] https://innovativegenomics.org/atf-report/

To what extent the cost of gene therapy and of targeted drugs can decrease is difficult to predict. An optimistic way is to look back at the cost of penicillin over 80 years ago – the data are difficult to find but a complete treatment (one week of injections) in 1940 would cost about $5,600. According to the consumer price index calculator this would be equivalent to $124,932.80 today; nevertheless, the cost today is $20 per week. The anti-HPV vaccine Gardasil still costs several hundred dollars almost 20 years after its introduction. Therefore, some costs go down but some stay the same, and it depends on how the value of the product is calculated.

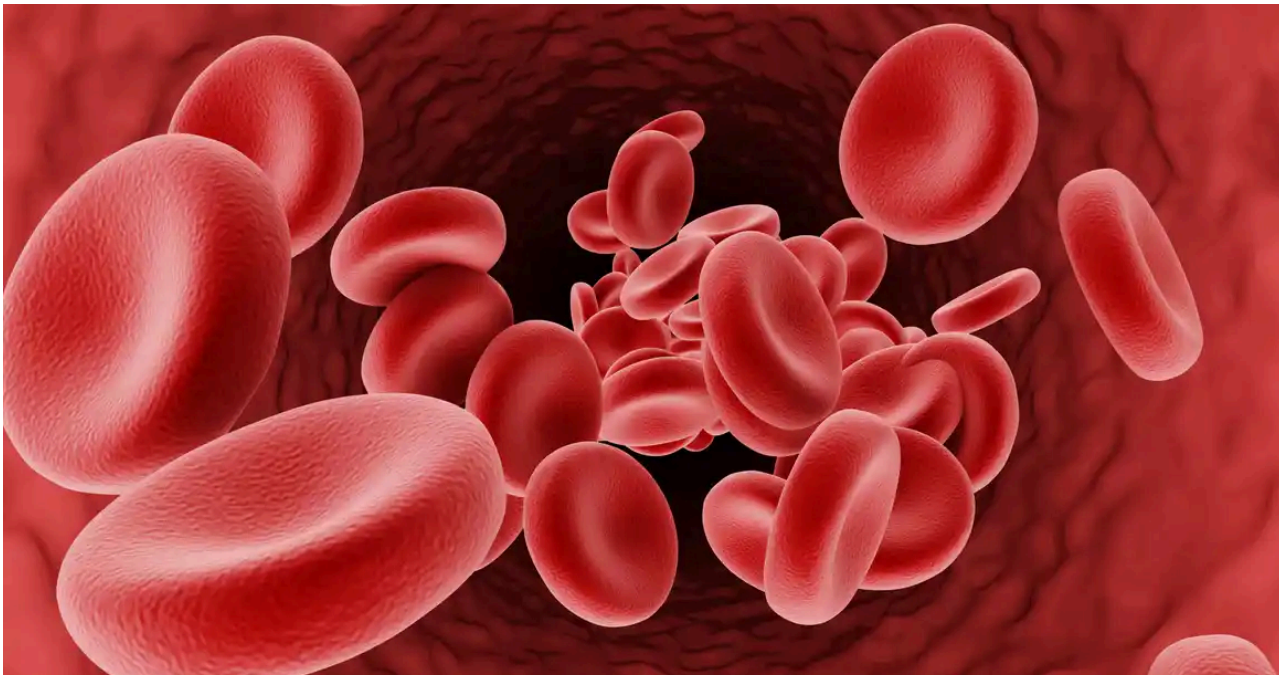
Nevertheless, genome editing technology was not developed to address health inequalities. There are many other available "simple" interventions that would have a great deal of impact and that humanity seems to choose to ignore. In that respect genome editing is a neutral entity .

Another approach is that described over 10 years ago by Rose [6], who pointed out that progress in medicine has been almost exclusively due to a trend towards relatively inexpensive interventions targeted to everyone, involving "clean air, water, effective sewage systems, pure food and programs of population-wide vaccination. The latter has already benefitted many people; most recently Covid-19 vaccines were estimated to have saved millions of lives. Of course vaccines, sanitation etc. are not a replacement for gene therapy, but they are interventions that can be more accessible to all.

Conclusion

Without some fairly dramatic efforts, the current crop of gene therapies will not result in global public health benefits, and to the extent that they become available at all, they will entrench existing inequities with respect to access to the best care.

[6] Rose, N. (2013). Personalized Medicine: Promises, Problems and Perils of a New Paradigm for Healthcare. Procedia - Social and Behavioral Sciences, 77, 341-352.



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