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How to pay for individualized genetic medicines

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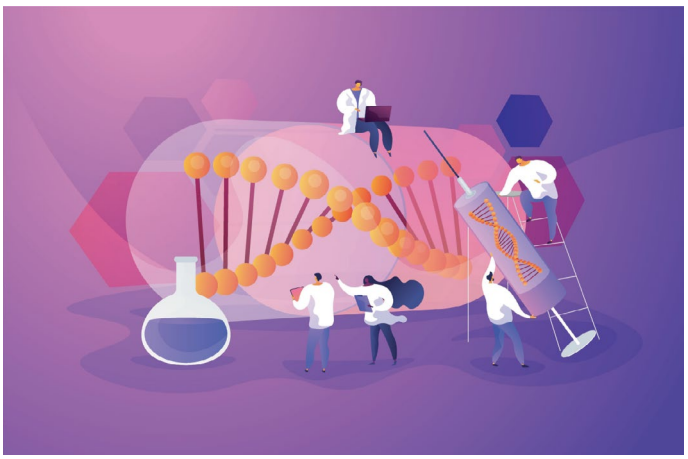
For precision genetic medicines to fulfill their potential as treatments for ultra-rare diseases, fresh approaches to academic–industry partnerships and data sharing are needed, together with regulatory change and adaptation of reimbursement models.



Advances in gene therapy and gene editing technologies could revolutionize the ability to treat individuals with genetic disease, allowing treatments to be devised that target specific genetic mutations in people with even the rarest of disease indications. In 2018, a seven-year-old child with Batten disease received attention for becoming the first recipient of a customized antisense oligonucleotide (ASO) therapy specifically designed for her unique mutation[1]. Since then, multiple patients with ultra-rare genetic conditions have been treated with precision ASOs[2–4] through academic-investigator-initiated programs.

Development of these ASOs has been rapid, justified by the severity of the conditions being treated (for example, rapidly progressive neurologic degeneration), following streamlined regulatory processes[5]. Here we discuss possible models for drug development, regulation and reimbursement that could allow these tailored genetic interventions to be scaled.

Paths to sustainability

Philanthropy has had a substantial role in piloting early efforts to develop individualized genetic medicines, supporting collaborations between academics, regulators, disease foundations and families. Scaling these efforts, however, is a substantial challenge. Tens of thousands of patients with ultra-rare diseases could someday be eligible for mutation-specific splice-switching ASO treatments[4,6]. When other gene therapies and gene editing techniques, such as small interfering RNAs and CRISPR editing of DNA or RNA, are taken into consideration, the number of patients who could be served by individualized genetic therapies increases to the tens of millions[7].

However, the small number of patients with each specific mutation precludes commercial viability under traditional biotech drug development models. Philanthropy alone will not be sufficient to address these unmet needs. To make individualized genetic therapies (sometimes called *n*-of-1 therapies) accessible, sustainable and equitable, systems for making them available must be developed.

Much may be learnt from history. Many of today's advanced routine medical practices were once cutting-edge interventions for small patient populations. In the mid-1900s, organ transplants were carried out only on rare occasions, typically between a patient and their next of kin at the time of death[8]. Today, organ transplantation is a life-saving therapy for over 40,000 patients annually in the USA alone. Expansion of transplant availability was catalyzed not only by advances in science and technology but also by local action, national data sharing and collaboration, regulatory change and insurance adaptation, lessons that may be applicable to the growth of individualized medicines too.

Cost of development

For the earliest individualized ASO projects, the cost of drug design, proof-of-concept efficacy testing, safety studies, manufacturing and clinical administration for 1–2 years have been estimated at US$1.4–2.0 million, with the majority of these expenses attributable to preclinical toxicology. Once developed, the cost of manufacturing a lifetime supply of an ASO may be as little as $40,000 per patient, although these figures are likely to change over time.

ASOs can be compared to existing medical interventions that are considered clinical standard of care. Organ transplants can cost up to $1.6 million; heart transplants are the most expensive and come with a 10–15% chance that the donor organ will be rejected by its new host[9] (Fig. 1). The gene therapy Lenmeldy (atidarsagene autotemcel), a lentiviral treatment for metachromatic leukodystrophy, has a list price of $4.25 million per patient[10]. Similarly, Biogen's Spinraza (nusinersen), an ASO for spinal muscular atrophy, has a list price of up to $4 million for a decade of treatment ($750,000 for the initial treatment and then $375,000 for each subsequent year). Efficiencies can be gained via collaboration, data sharing and regulatory innovation, each of which will reduce costs.

Collaboration and data sharing

For organ transplants, collaboration between academic institutions has allowed the matching of viable organ donors to recipients, as well as

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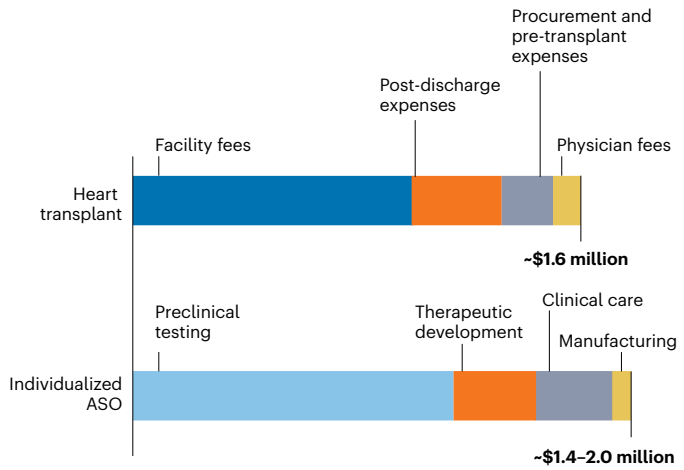

Fig. 1 | The comparable costs of transplantation and gene therapy. Total billed charges for average US heart transplants are comparable to total development expenses for individualized gene therapies such as ASOs. Transplant costs comprise charges billed for hospital and physician services, organ procurement, 30 days pre-transplant preparations, readmissions 180+ days post discharge and post-operative immunosuppressive therapy (data from 2020). Costs for ASOs include development, toxicology and clinical testing, and manufacturing (data from 2019–2020). Source: 2020 Milliman U.S. Organ and Tissue Transplants Research Report and Yu laboratory.

the development and refinement of best medical and procedural practices to allow the expansion of transplantation. The Transplantation Society was the first formal body to assemble key stakeholders, including physicians and scientists, together in 1966; they shared knowledge through symposia and the creation of the journal, *Transplantation*. Pharmaceutical industry professionals also joined and were key to the development of immunosuppressive drugs[8]. Not only did the Transplantation Society allow the exchange of ideas, scientific findings and best practices, but when living organ donation began to be exploited for profit, the Transplantation Society took an ethical stand in 1985, condemning the sale of organs and publishing stringent guidelines against these practices. In this manner, academics at the cutting edge of transplant science and clinical practice played a key role in consolidating best practices, as well as providing a critical set of checks and balances against the potential of exploitative commercialization, all to serve patients better.

The history of organ transplantation provides a lesson on the importance of data sharing and collaboration in the implementation of novel treatment paradigms. In 1977, the United Network for Organ Sharing (UNOS) was created to establish the first computerized system for matching donors and recipients across patients in the southeastern USA[11]. In 1984, UNOS was incorporated into an independent nonprofit and became responsible for operating the Organ Procurement and Transportation Network (OPTN), a national network responsible for the allocation of organs and collection of donation, transplant and patient outcomes data nationwide[11].

For individualized therapies, such as ASOs, there is a compelling need to openly share learnings and to optimize the efficiency, safety and efficacy of this technology for patients. Independent nonprofit organizations can help convene academia, industry and regulatory stakeholders, facilitate learning and data sharing, and align the incentives of each actor to advance therapy accessibility for patients.

Regulatory innovation

Regulatory and legislative innovation will be needed to support the rollout of this technology. In transplant, the creation of the OPTN was spurred by the National Organ Transplant Act of 1984 (NOTA). Legislative tailwinds are just beginning for individualized genetic therapies, with increasing recognition of the need to create different regulatory paradigms to support them[12]. The US Food and Drug Administration (FDA) released draft guidance in 2021 defining streamlined development processes for *n*-of-1 ASO trials[5], and regulatory leadership has been vocal about supporting platform technologies and increasing the use of accelerated approval for gene therapies for rare conditions.

In 2023, the FDA Modernization Act 2.0 eliminated the formal requirement that drugs in development must be tested in animals before being used in clinical trials (creating legal windows for accelerating development, with increased use of in silico or in vitro models)[13]. These moves can be optimistically interpreted to reflect early legal and regulatory positioning that may allow gene therapies to be deployed at a broader scale, should the science allow.

If regulatory frameworks can be expanded to accommodate platform efficiencies, it may be possible to envision a business model in which sustainability can be generated from smaller margins on a portfolio of many different treatments, rather than relying on the success of one or two blockbuster molecules. Potentially supporting this notion, the probability of success of rare-disease therapeutics has been documented to be higher than average, most likely because of the highly targeted nature of these medical interventions, coupled with greater understanding of disease biology; this implies higher expected earnings than projects with lower probability of success[14]. Ultimately, in individualized genetic medicine, the product is not the actual molecule, but rather the process of development, administration and monitoring.

Future funding models

Funding is needed to accelerate advancement of novel treatment paradigms. A key inflection point in the growth of organ transplant in the USA was Medicare coverage of kidney transplantation. Reimbursement offerings by Medicare, Medicaid and private insurers have allowed transplant to be a widely available treatment option today[11].

Innovative payment models may be needed to smooth the path to reimbursement, given relatively high upfront costs. One proposal for reimbursement of individualized genetic therapies is to view the development of the therapy as a procedure, requiring the creation of an Interventional Genetics subspecialty that generates revenue like a procedural department, billing for performing the process of gene therapy development. In such a paradigm, the price of ASO development (the procedure) could be set for each combination of therapeutic area and modality; this would be an average of the previous cost of gene therapy development in each category, plus an agreed-upon additional margin to further incentivize development. Maintenance therapy would then be sold at manufacturing cost plus a small markup. This model may be difficult to implement, as payors often have different departments to manage therapeutics and procedures, and it requires the adoption of a new payment paradigm and agreement on set prices for an inherently individualized intervention.

A subscription payment model has been successfully deployed to allow access to the innovative and curative hepatitis C drug Sovaldi (sofosbuvir), for which high upfront costs were required for a relatively small number of patients, each of whom would have substantial ongoing healthcare usage[15]. This model could also be used for

individualized genetic therapies because it decouples the number of patients being treated from the potential financial reward, thereby making ultra-rare diseases possibly commercially viable.

A subscription fee, ideally borne by a payor (such as the government or an insurance company), would be paid to a center of excellence or suitable commercial organization. This fee would allow patients covered by that payor to be candidates for treatment at no additional cost. Predictable subscription revenue for academic centers of excellence would allow innovation to continue, making development more efficient and providing funding for time-sensitive development projects for patients with rapidly progressive disorders. Commercial developers would also benefit from the more predictable stream of earnings from subscription fees, which, if the company is public, could lead to higher stock market valuations.

Coordination between academics and industry is needed, not only for cost efficiency but also because negotiation with payors on price (subscription or otherwise) is likely to happen on an organization-by-organization basis. Next steps for the field should include an analysis of existing cases to understand the safety, efficacy and cost savings of individualized genetic therapies, a more efficient process to identify patients who could benefit from these therapies, and an analysis of existing healthcare costs for such patients, to build the case for insurance coverage and private- and public-sector funding.

Conclusion

Individualized genetic therapies are now scientifically possible, providing hope for many patients with ultra-rare diseases previously deemed too rare for traditional drug development. To make these therapies routine, new systems must be built to allow these medicines to be equitably and sustainably delivered. Costs are high, though on the same order of magnitude of similar life-altering but high-risk procedures such as transplant, and below the prices of numerous commercial gene therapies on the market.

With proper commitment, costs can decrease as efficiencies, garnered from data sharing and regulatory innovation, reshape the development landscape. Innovative payment models, including subscription models and procedural billing, should be investigated. With further scholarship and collaboration between stakeholders, individualized genetic therapies can become an accessible therapeutic option for many patients in need.

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References

1. Kim, J. et al. *N. Engl. J. Med.* **381**, 1644–1652 (2019).
2. Korobeynikov, V. A. et al. *Nat. Med.* **28**, 104–116 (2022).
3. Tran, H. et al. *Nat. Med.* **28**, 117–124 (2022).
4. Kim, J. et al. *Nature* **619**, 828–836 (2022).
5. US Food & Drug Administration. *Draft Guidance for Industry* https://go.nature.com/3RimwVu (December 2021).
6. Nguengang Wakap, S. et al. *Eur. J. Hum. Genet.* **28**, 165–173 (2020).
7. Richter, T. et al. *Value Health* **18**, 906–914 (2015).
8. The Transplantation Society. *Four Decades of International Cooperation, Innovation, Growth and Progress* https://go.nature.com/4aYWU76 (2006).
9. Bently, T. S., Ortner, N. Milliman (2020).
10. Manalac, T. *BioSpace* (20 March 2024).
11. US Health Resources & Services Administration. *Organ Donation and Transplantation Legislation History* https://go.nature.com/3RhbYWm (April 2021).
12. US Congress. H.R. 2617: Consolidated Appropriations Act, 2023 (2022).
13. S.5002 - FDA Modernization Act 2.0. 17th Congress (2021–2022).
14. Wong, C. H., Siah, K. W. & Lo, A. W. *Biostatistics* **20**, 273–286 (2019).
15. Auty, S. G., Griffith, K. N., Shafer, P. R., Gee, R. E. & Conti, R. M. *J. Health Polit. Policy Law* **47**, 691–708 (2022).

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Competing interests

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