

A roadmap for affordable genetic medicines

<https://doi.org/10.1038/s41586-024-07800-7>

Received: 22 November 2023

Accepted: 9 July 2024

Published online: 17 July 2024

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Twenty genetic therapies have been approved by the US Food and Drug Administration to date, a number that now includes the first CRISPR genome-editing therapy for sickle cell disease—CASGEVY (exagamglogene autotemcel, Vertex Pharmaceuticals). This extraordinary milestone is widely celebrated owing to the promise for future genome-editing treatments of previously intractable genetic disorders and cancers. At the same time, such genetic therapies are the most expensive drugs on the market, with list prices exceeding US\$4 million per patient. Although all approved cell and gene therapies trace their origins to academic or government research institutions, reliance on for-profit pharmaceutical companies for subsequent development and commercialization results in prices that prioritize recouping investments, paying for candidate product failures and meeting investor and shareholder expectations. To increase affordability and access, sustainable discovery-to-market alternatives are needed that address system-wide deficiencies. Here we present recommendations of a multidisciplinary task force assembled to chart such a path. We describe a pricing structure that, once implemented, could reduce per-patient cost tenfold and propose a business model that distributes responsibilities while leveraging diverse funding sources. We also outline how academic licensing provisions, manufacturing innovation and supportive regulations can reduce cost and enable broader patient treatment.

Cell and gene therapies (CGTs), also referred to as genetic therapies, are transformative in the context of monogenic disease and cancer^{1,2} and could further provide ground-breaking advances in disease prevention^{3,4}. These therapies modify a patient's gene, gene expression or the biological properties of cells for therapeutic use^{5,6}. Approvals by the US Food and Drug Administration (FDA) are steadily increasing, with hundreds of products in development⁷. The platform nature of the underlying technologies⁸, along with the ability to precisely correct specific genetic defects, now render much of the human genome 'drug-gable'. However, multi-million-dollar price tags raise concerns about who will benefit from therapeutic advancements and whether payers are prepared to provide such large, one-time payments^{9,10}. The failure of commercial entities to bring safe and effective genetic therapies to market¹¹, to reach agreement on prices with payers¹² and difficulties with company viability¹³ point to larger compatibility challenges between this class of interventions and the healthcare ecosystem (Fig. 1). With the advent of successful clinical applications of CRISPR-based approaches across a number of distinct disease indications¹⁴, these challenges are especially acute.

A recent model simulated that 18 out of 109 US-registered late-stage gene-therapy clinical trials in phase II or III will be approved between 2020 and 2034, costing an annual US\$20.4 billion under conservative assumptions¹⁵. Today, developers must contend with limited availability of critical reagents at current good manufacturing practice (cGMP) grade, insufficient manufacturing capacity and expensive process

transfers to commercial-grade manufacturing—factors that could halt further development^{16–18}. On the payer side, eligibility restrictions in the United States dictate who gains access to genetic therapies. As reviewed in a recent assessment of state Medicaid coverage practices in the United States, gatekeeping disproportionately affects low-income Americans⁹, a reality brought into sharp relief by the recent approvals of CASGEVY and LYFGENIA for sickle cell disease, which primarily affects individuals of African descent^{19,20}. Access in low- and middle-income countries (LMICs) is an even greater challenge^{21–23}. Despite these numerous obstacles, the outsized therapeutic benefits derived from addressing the genetic root causes of disease highlight the societal imperative of advancing genetic therapies. Innovative, system-wide solutions are needed now if we are to realize the full promise of CGTs.

Here we provide a roadmap for a comprehensive solution to this challenge based on the research and recommendations of a multidisciplinary task force of experts and practitioners who evaluated alternative development frameworks to take genetic therapies from discovery to market¹⁰. The proposed solutions address intellectual property management, regulations, manufacturing technology, pricing and business models that taken together could reduce costs and expand access. Note that, while policy intervention is a critical tool to effect system-wide change, we excluded recommendations that would necessitate regulatory changes from the scope of task force deliberations and instead focused on changes that can be implemented by the key players within the ecosystem (Fig. 1).

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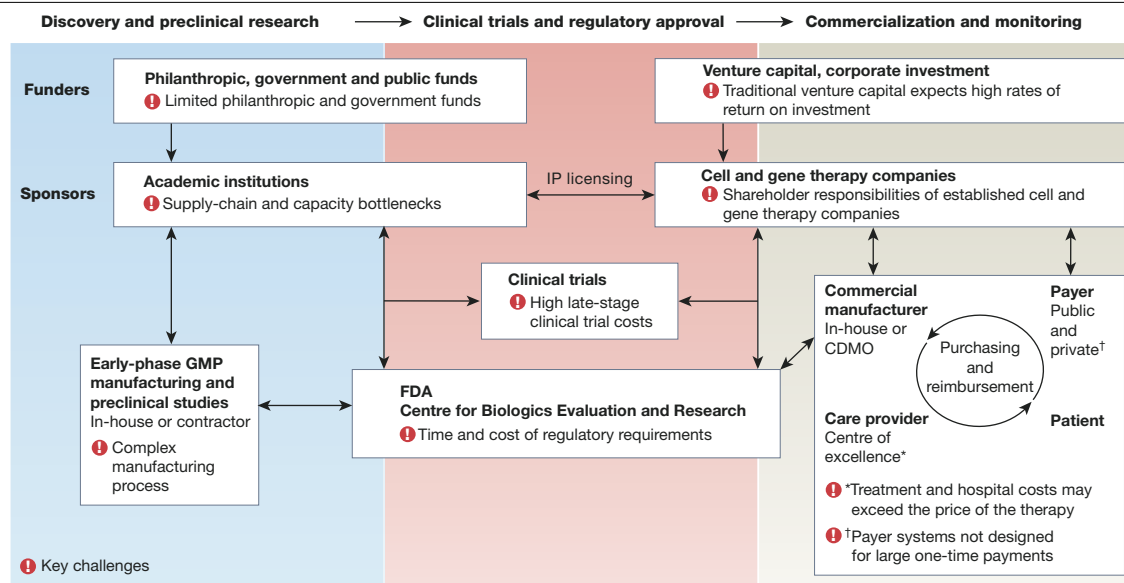


Fig. 1 | Key stakeholders and challenges in genetic therapy development.

A genetic therapy generally originates in academic institutions and culminates in patient treatment with an approved medicine, with unique challenges at each step. Academic institutions are well-positioned to drive initial discovery efforts through to IND-enabling studies and, in a number of cases, phase I/II trials. They are typically funded by government and philanthropic grants that require no financial return on investment; however, these grants provide only a portion of the multimillion-dollar cost of bringing a genetic medicine to licensure. Pivotal clinical trials in the genetic therapy space are conducted by pharmaceutical or biotechnology companies who license patent rights from academic institutions, with typical costs of attaining approval exceeding US\$25 million even for rare disease indications. Publicly traded pharmaceutical companies have a fiduciary responsibility to maximize

shareholder value, while startups are backed by venture capital investors who seek high rates of return on investments. Commercial-scale manufacturing can be carried out in house by large pharmaceutical companies or at a contract development and manufacturing organization (CDMO) to reduce costs by centralizing expertise and infrastructure. Sponsors of an FDA-approved therapy typically assemble a treatment team under the auspices of a care provider (that is, centre of excellence). This medical centre helps patients to navigate insurance coverage, orders the drug product and oversees staff training. Patients may spend months at the centre during multi-step treatments, so social services are critical for delivering the therapy and may include housing, transportation and day-to-day costs during these extended stays. GMP, good manufacturing practice; IP, intellectual property.

Negotiating access through licensing agreements

Academic research groups drive discovery and early preclinical work with support from government grants (Fig. 1). Indeed, all approved genetic therapies trace a formidable portion of intellectual property to academia²⁴, meaning that, collectively, academic institutions have considerable leverage. Academic technology transfer offices (TTOs) could exercise that leverage by incorporating legally binding access provisions into licensing agreements.

On average, biologic drugs in the United States are 3.59 times more expensive than in peer countries²⁵. For example, the approved gene therapy ROCTAVIAN (valoctocogene roxaparvovec-rvox, BioMarin) has a US price of US\$2.9 million but, in Germany, the price is US\$1.5 million²⁶. As has been demonstrated recently, access provisions could institute a 'most-favoured nation' clause that would ensure that US patients do not pay more than patients in economic peer countries^{27,28}, or could include support for particular US populations (for example, low-income individuals, under- or non-insured people and Medicaid beneficiaries).

License agreement provisions could also require price reductions once certain volumes are sold, or substantially increased royalties could be triggered in the absence of volume-based price reductions, similar to provisions in the Inflation Reduction Act of 2022 (ref. 29). To discourage therapies being shelved while companies retain intellectual property rights, exclusive licenses could automatically convert to non-exclusive licenses if development is not continued within negotiated time periods. Such license conversion could also occur if post-approval studies for a therapy are not conducted in a timely manner or if additional drug development for new indications does not progress. In LMICs, pharmaceutical manufacturers rarely seek marketing authorization

or establish distribution channels. Access plans could include requirements to develop licensed, affordable products that are registered in all needed markets in a timely manner. Alternatively, licenses could be made non-exclusive in LMICs if licensees are unable or unwilling to supply a therapy. Furthermore, licenses could be granted directly to third-party organizations, such as the United-Nations-backed Medicines Patent Pool (<https://medicinespatentpool.org/>), which works to increase access through patent pooling and voluntary licensing. Licensees could agree to work with these third-party organizations as a means to achieve their access obligations.

While changes to licensing practices are theoretically immediately actionable, academic institutions face an inherent tension between their public benefit mission and financial incentives to maximize licensing income to supplement institutional operating costs. As the success of TTOs is in part measured by the number of agreements signed and royalties received³⁰, these offices may be concerned that potential licensees will reject access provisions and opt to work with other universities who provide more favourable terms. In 2007, several major universities signed onto a document known as 'Nine Points to Consider' about university patent licensing processes that was developed by the Association of University Technology Managers³¹. This document urged the adoption of access provisions that would benefit neglected patient populations. However, a recent analysis found that the Nine Points document resulted in "...few changes relating to the promotion of public or access to medical technologies" because few institutions adopted the recommendations related to accessibility and affordability³². Thus, universities should collectively strive to develop common frameworks for access across academic institutions and university leadership should lend wholehearted support for these practices. Publication of licensing agreements with minimal redactions

(to protect commercially sensitive information) would set new norms for the inclusion of affordable access provisions among universities. Shifts in this direction are emerging, with knowledge of key issues, including data on access across diverse geographies and socioeconomic groups, and the use of dedicated tools spreading^{33,34} (for example, the MAPGuide Equitable Access Toolkit; <https://go.nature.com/4djtMs8>). Meaningful change will require university trustees to empower TTOs to both implement licensing access plans and enforce them, and will need major academic institutions to work together such that access obligations in patent licenses become the norm.

Regulatory and manufacturing innovation

Developers of genetic therapies face high costs of goods, limited manufacturing capacity and stringent quality requirements for all components of the genetic medicine (for example, guide RNA, lipids used in nanoparticles). Academic facilities that meet phase-appropriate cGMP requirements often enable first-in-human investigations of genetic therapies and are essential contributors to a thriving CGT ecosystem.

Comparability challenges

Process transfers from academic to commercial-grade manufacturing necessitate extensive comparability assessments, which, in some cases, have halted product development¹¹. The FDA assesses comparability of the pre- and post-change drug product on quality attributes such as identity, quality, purity and potency. Comparability assessments require validated analytical assays for each product and, depending on how advanced in development a CGT is, additional clinical studies³⁵. This is particularly onerous for genetic therapies produced in academic cGMP facilities and tested in a small number of individuals in phase I/II trials. For example, the transfer of manufacturing processes to commercial grade of a new investigational ex vivo lentiviral therapy shown to be safe and curative in 50 individuals with adenosine deaminase deficiency (ADA-SCID: 100% overall survival ≥ 24 months after treatment)³⁶, is estimated to cost US\$30 million–40 million at a contract development and manufacturing organization (personal communication with D. B. Kohn). For a disease that affects around 10 patients per year in the United States and Canada, this is a tremendous financial burden of little commercial interest to for-profit biotechnology companies^{11,37}.

In its recently published draft guidance on comparability assessments for CGT products, the FDA points out that “transferring... to a new manufacturing facility is generally considered a major change that may require extensive comparability evaluation”³⁵. This affects most academically developed products. In this draft guidance, the agency further provides examples of changes that would result in the need to submit a new investigational new drug (IND) application; however, developers would also benefit from examples of the types of changes that would not require new IND submissions and greater detail on how to demonstrate comparability.

While putting patient safety first, risk–benefit considerations should be used in the case of products for severe disease with substantial morbidity and mortality and in cases in which early-stage clinical data show robust safety and efficacy^{36,38,39}. A risk-based comparability approach that relies on experimental evidence and considers modality-specific risks could reduce the regulatory burden. For example, regulators may consider that changes to the purification method of a lentivirus used to transduce stem cells ex vivo carry less risk than similar process changes for an AAV that is intended to be administered systemically, and lessen the comparability requirements accordingly.

Innovative solutions

Designating well-characterized manufacturing processes as platforms would be particularly helpful in mitigating the cost and labour intensity of current regulatory requirements. The leadership of FDA's Center

for Biologics Evaluation and Research has enunciated a vision for leveraging the platform nature of genetic therapies by using nonclinical information between ‘parental’ and ‘offshoot’ products that differ in only one component (for example, the guide RNA)⁴⁰. This would remedy the status quo, wherein a single change to engineer a new genetic medicine for severe disease—an approach that the fundamental nature of CRISPR gene editing technology enables—extends the manufacturing timeline beyond the lifespan of the patient. Recently, the agency published draft guidance that describes a pathway for a sponsor to obtain a platform technology designation for a well-understood and reproducible technology that can be incorporated into more than one drug product to increase efficiencies without resulting in adverse effects on quality, manufacturing or safety⁴¹. Notably, the draft emphasizes the need for the technology to have previously been used in an approved product and limits use of the designated platform technology to the same sponsor, or an entity that has obtained approval from that sponsor, raising questions about its utility in academic settings and drug development for ultra-rare diseases.

Regulatory authorities, academia and industry should collaborate closely to establish streamlined protocols that are open source to provide iterative safety data and avoid duplicating efforts. An initiative to establish open-source manufacturing protocols was recently funded by the California Institute for Regenerative Medicine⁴². Government programs such as the Somatic Cell Genome Editing program⁴³, the Bespoke Gene Therapy Consortium (<https://go.nature.com/3BitDrM>) and the Platform Vector Gene Therapy pilot (<https://pave-gt.ncats.nih.gov/project-overview/>) are important contributions towards achieving this goal.

Academic centres often develop therapies for individuals with ultra-rare disorders that are of little to no commercial interest. In some cases, such efforts yield exceptionally high clinical benefit, with around 100% of the participants in several studies experiencing resolution of major disease symptoms^{1,36,38,39}. One possible approach to enable access to genetic medicines for ultra-rare disorders would be for regulators to permit continuous treatment under phase-I-appropriate cGMP standards and clinical protocols (a perpetual IND). Early-phase requirements are deemed by the FDA sufficient to allow studies in human individuals, with adequate informed consent, monitoring and adverse-event reporting in place⁴⁴. In the case of CGTs, close follow-up of participants can provide important evidence of safety and efficacy that may inform a therapy's risk–benefit profile. Given the very small patient populations and substantial resources needed to obtain an IND for a genetic therapy, such a framework poses minimal risk to public health and is unlikely to be abused.

Beyond regulations, cGMP-grade critical reagents are prohibitively expensive for the vast majority of academic manufacturing groups. Robust supply chains are essential to support the development of non-viral delivery methods for gene modification that require fewer resources and have lower batch-to-batch variability relative to viral vectors^{45,46}. Distributed manufacturing is another innovative model to reduce manufacturing costs and increase access. Traditionally, drug manufacturing is conducted at centralized sites but, for autologous cell therapies, this model is logistically onerous and may reduce efficacy due to cryopreservation⁴⁷. In the point-of-care model (a type of distributed manufacturing), a treating hospital or local cGMP facility produces the cell therapy product, allowing for rapid administration of the modified cells in patients⁴⁷. Closed, automated manufacturing has a critical role in implementing distributed manufacturing. By reducing the need for clean rooms and highly trained staff, such systems could be deployed in underserved regions to expand access at lower cost. The Made-in-Canada CAR-T program (<https://go.nature.com/4ed9emo>), which produces cell therapies at a tenfold lower cost than the commercial option, is a prime example of the impacts that a distributed manufacturing model with government backing can have on affordability and access⁴⁸ (N. Prokopenko, personal communication).

Table 1 | The 10× less model

Item	Assumption	Calculation	Cost per patient
Number of patients per year	2,000		
Time horizon to recover R&D costs	7 years		
Manufacturing costs per patient	US\$100,000		US\$100,000
Annual fixed production and marketing	US\$75 million	Divide the annual costs by the number of patients per year	US\$37,500
Manufacturing plant construction	US\$200 million	Divide the one-time fixed cost by the number of patients over time horizon	US\$14,290
R&D costs to recover	US\$1 billion	Divide the R&D costs by the number of patients over time horizon	US\$71,430
Cost of capital	8%	Divide the average annual cost of capital by the number of patients over time horizon	US\$20,993
Net profit	US\$200 million	Divide the net profit by the number of patients over time horizon	US\$14,290
Estimated sustainable price			US\$258,500

A hypothetical organization wishes to treat an average of 2,000 patients per year within 7 years on the market, the Orphan Drug Exclusivity period granted by the FDA for rare-disease therapies. In this example, manufacturing costs of the therapy are assumed to be US\$100,000 per treatment. Annual fixed costs of operations and marketing (including physician education) are US\$75 million and there is a one-time fixed cost of building and equipping a manufacturing plant of US\$200 million. The organization wishes to recover R&D costs of US\$1 billion at an 8% cost of capital. At this cost of capital, US\$20,993 is added to the price per patient so that the present discounted value of the profit stream over 7 years is equal to US\$1.2 billion (R&D costs of US\$1 billion plus the manufacturing plant of US\$200 million). A US\$200 million profit is also included. Spreading the costs across 2,000 patients per year for 7 years brings the sustainable price of the therapy to US\$258,500 per patient. If a priority review voucher is awarded, it could be sold for around US\$110 million; however, as this is not a guarantee, we chose not to include it in this example.

Although point of care manufacturing through mechanisms such as a local hospital exemption is lowering prices in other countries^{23,49,50}, this has been challenging to implement in the United States under existing regulatory frameworks^{47,51}.

The price is wrong

The most obvious question is: why are the prices for CGTs so high? Second, what is a reasonable price to ensure that life-saving therapies continue to be developed while not overburdening payers, patients and the healthcare system⁵²?

For-profit companies have a fiduciary responsibility to maximize shareholder value, and the high prices of CGTs reflect the maximum profit companies estimate they can garner from the market. At the same time, companies often cite value-based pricing to explain the high prices of genetic therapies^{53–55}. Value-based pricing bases the price of a drug on its cost-effectiveness and the magnitude of its benefits to patients, the healthcare system and society⁵⁶. In itself, the value-based pricing approach raises numerous concerns, including valuations set in comparison to already inflated healthcare costs and companies setting prices at the full value the therapy is supposed to confer to society, among others⁵⁷. Most importantly, value-based prices are not set in relation to the cost of development and production¹⁰. This means that technological advances that lower the cost to manufacture and deliver the therapy will not necessarily result in lower prices for patients and

Table 2 | Key considerations for alternative business models

Organization type	Advantages	Disadvantages
Non-profit organization	Mission focus Tax-exempt Grant and philanthropically funded Greater public trust	Difficult to raise funding Ineligible for business funding programs Challenges compensating talent Limits on commercial sales MROs only; active research required
501(c)(3) MRO		
501(c)(4) Social welfare organization		
PBC	Public benefit mission legally protected Diverse sources of revenue Attractive to investors Limited liability Profits support sustainability	Can convert to C-type corporation For-profit corporation tax rate Onerous reporting requirements Lower returns/profits
Government-backed entity	Substantially lowers costs to (public) healthcare systems Stable, low-cost financing Government co-ordination on clinical development and regulations	Substantial infrastructure investment Administrative/logistical complexities Country specific
Opportunities and challenges for non-profit entities, PBCs, government-backed initiatives and mixing of models.		

payers. Even with a pricing framework that prioritizes affordability, insurance coverage will be necessary. Insurers in the United States will cover treatments between US\$50,000 and US\$250,000 without additional scrutiny or coverage limitations⁵⁸.

We evaluated several pricing philosophies (for example, cost-plus, portfolio-based approaches) as well as payment models (such as subscription, outcome-based pricing, healthcare loans)^{59–62}. A key assumption in developing a new pricing model is that there must be enough revenue that the entity developing the drug could become self-sustaining. A pricing philosophy that ties the final price of a product to the cost of development and deployment, while ensuring maximum insurance coverage, delivers the lowest cost to patients (Table 1).

Despite a scarcity of concrete data, widely cited studies put the capitalized cost of research and development (R&D) of a new drug between US\$314 million and US\$2.8 billion (with a cost of capital between 7% and 11%, including failures)^{63–65}. An analysis of 63 drugs approved by the FDA between 2009 and 2018 found a median cost of capitalized R&D of US\$1.14 billion (including failures)⁶³. In the model presented in Table 1, we estimate that US\$1 billion for drug development costs is sufficient to account for investment in failed projects and assumed an 8% cost of capital (this figure is used by the Centers for Medicare & Medicaid Services in its implementation of the 2022 Inflation Reduction Act to determine whether a for-profit brand-name drug manufacturer has recouped drug development costs⁶⁶).

The cost to build and adequately equip a manufacturing plant that can produce autologous therapies ranges from several million to hundreds of millions of US\$ in the published literature, with variability dependent on the facilities’ size, location and project-specific factors^{67–70}. The upfront construction and equipment costs of a facility with the capacity to produce 500 to 5,000 batches per year was estimated at US\$200 million for the model^{69,71}, a figure confirmed as a reasonable estimate by the combined expertise of task force members with many years of experience in manufacturing CGTs (Supplementary Table 1). Operating costs for a cell therapy were estimated to be between US\$8,000 and US\$23,000 per patient^{69,72}; extrapolated to 2,000 patients per year, this is a fixed production cost of US\$16 million to US\$46 million. Selling, general and administrative costs can be considerable, and the 15 largest biopharmaceutical companies spend more on these activities than R&D⁷³, ranging from 24.5% to 51.9% of revenue in 2022 (ref. 74). This model (Table 1) estimates

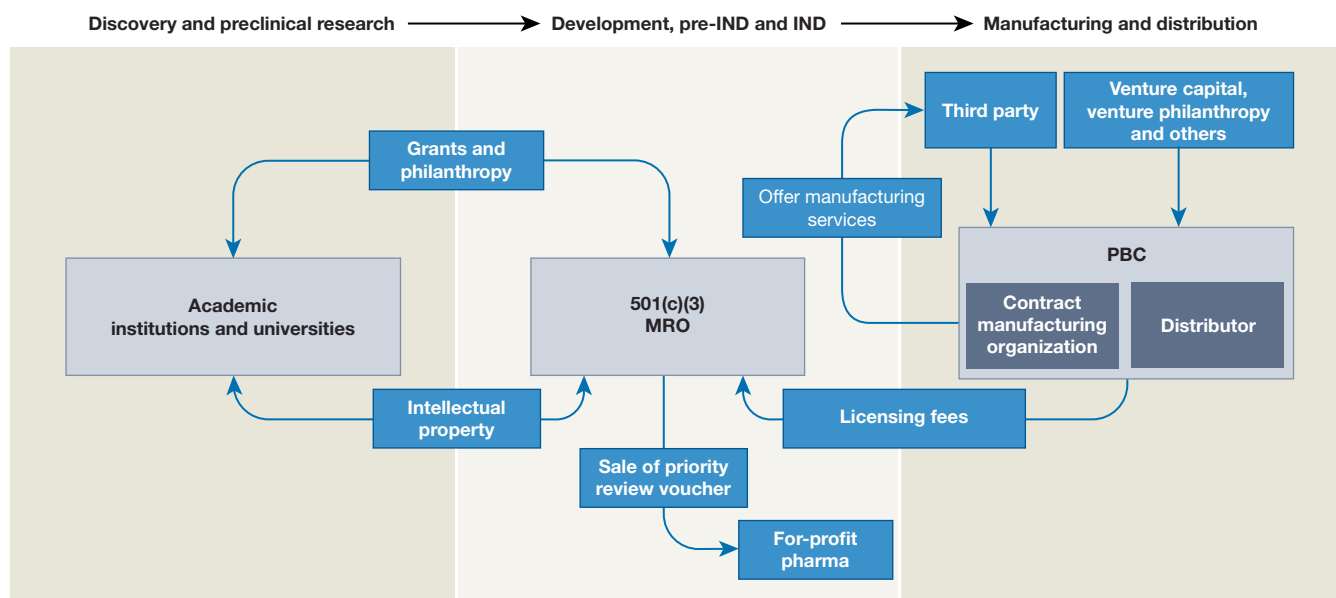


Fig. 2 | Hypothetical alternative organization using a mixed model. In this model, an academic institution conducts discovery and early preclinical work using philanthropic or government funding that requires no or low return on investment. The intellectual property is transferred to an MRO to develop and translate the product. The MRO would, among other duties, handle FDA filings, manage or outsource clinical trials, oversee commercial contracts and hold the legal permissions to commercialize a CGT. The benefit of an MRO is to bring together the expertise needed to run professional clinical trials, which is distinct from the know-how commonly found in academia. In the United States,

the MRO would be able to sell a priority review voucher to raise funding. The MRO would license the approved product to a PBC for commercial manufacturing and distribution. In addition to revenue from sales of the product, the PBC can take investments from venture capitalists and generate revenue by offering manufacturing capacity to commercial partners. While being separate legal entities, the organizations could have overlapping boards of directors who would assure that co-ordination is a top priority. In this example, the MRO (a non-profit organization) controls the intellectual property and can make decisions on priorities that are not purely profit driven.

US\$75 million of annual fixed production and marketing cost, which would amount to approximately 37.5% of revenue generated by year seven. The cost of goods is also difficult to estimate and is product specific. For CAR T cell therapies, for example, published values for the cost of goods range between US\$60,000 and US\$90,000 per dose^{24,75,76}.

Typically, an approved drug will generate revenue over a period of at least 12 to 15 years, or until generic or biosimilar competition takes place. For drugs with orphan drug designation, the FDA guarantees an exclusivity period of 7 years, meaning that it will not approve another product for the same indication with the same active moiety⁷⁷.

Sensitivity analysis

Components of the model can be modified to recover higher drug development costs or to treat more patients. For example, if an organization seeks to recover US\$2 billion for drug development, the price would increase by 26% to US\$347,415 per patient. Pricing under this framework is sensitive to the number of patients expected to receive the therapy each year; a treatment for an ultra-rare disease affecting 200 people per year that costs US\$1 billion to develop would require a per-patient price of US\$1.68 million. If the drug was administered to 10,000 patients per year, its price would drop to US\$132,699 per patient. Organizationally, this underlines the importance of a diverse portfolio of products, whereby profits from therapies with larger patient populations can be used to subsidize the cost of bespoke therapies for ultra-rare diseases.

Although there is uncertainty in the cost to build and operate a CGT facility^{67–70}, these values have a smaller impact on prices than the number of patients. If the manufacturing facility costs US\$4 million, the estimated sustainable price would be US\$241,064 while at the higher end of the reported range at US\$861 million, the cost per patient would be US\$317,270. The time horizon over which development costs are recovered and profits are calculated can be extended. In this model,

any profits generated after the initial 7 year period (US\$242 million per year) would not be needed to repay investors.

This illustrative framework is intended to show how tethering price to the cost of development, manufacturing and deployment can advance affordability and accessibility goals while keeping sustainability in mind (Table 1). As this framework does not aim to maximize profits, it is unlikely that an entity considering this approach will be a traditional for-profit organization.

A new way of doing business

To successfully implement innovative pricing models, creative business solutions and funding arrangements are essential⁷⁸. We reviewed organization types including 501(c)(3) charitable organizations, 501(c)(4) social welfare organizations, medical research organizations (MROs), public benefit corporations (PBCs) and mixed models of multiple aligned organization types with governance structures that ensure mission alignment (Table 2).

The most common alternative business models of pharmaceutical R&D are public-private product development partnerships, which have successfully launched over 50 products to the market over the past two decades for neglected diseases such as tuberculosis, malaria and cholera⁷⁹. In these arrangements, a non-profit organization typically integrates a mix of public and private capital and expertise around a mission of affordability and access, thus demonstrating the feasibility of non-commercial approaches⁸⁰. Among organizations that the task force engaged, those applying mixed models were more common; these included Medicines360, a non-profit MRO that distributes and commercializes products globally through an LLC subsidiary, ImpactRH360, and in the United States through the for-profit organization CuraePharma (<https://medicines360.org>). Furthermore, Civica Rx, a 501(c)(4) organization, has successfully tackled generics shortages through a healthcare utility model, and has established a philanthropic

Box 1

The Priority Review Voucher program

The priority review voucher (PRV) program was first passed by the US Congress in 2007 as an incentive program designed to support the development of drugs for neglected tropical diseases⁹⁰ and has since been extended to rare paediatric diseases⁹¹. After approval of an eligible drug, the FDA grants the sponsor a PRV, which may be used in the future to expedite the review process of a non-PRV-eligible drug or biologic by about 4 months. This can translate to hundreds of millions of dollars worth in sales for blockbuster drugs. PRVs can also be sold to other entities and have been valued as high as US\$350 million⁹¹. In recent years, the valuation of PRVs appears to have stabilized, with vouchers for rare paediatric diseases sold at an average price of US\$100 million in the 2020–2023 period⁹². Vouchers can have an important role in business decisions, with one non-profit company relying entirely on profits from the sale of its PRV⁹¹. By contrast, several research studies, covering the period of 2009–2019, found only slight, if any, impacts of PRVs on increased development of drugs for the various eligible categories^{93–96}. The future of the program is uncertain, given the mixed reports of their incentivizing effects, increasing supply (and therefore reduced value) and strain on FDA staff to manage the program and accelerate reviews^{91,93,94,97}. Congress could let the PRV program for rare paediatric diseases lapse if it chooses not to reauthorize it by the end of September 2024. PRVs are only part of the incentives offered for rare disease drug development, and approvals of these drugs have risen from 25% of FDA approvals during the 2001–2005 period to 48% during 2016–2020, thanks to tax breaks, fee reductions and longer market exclusivities, among other incentives^{73,98}.

arm (Civica Foundation, 501(c)(3)) as well as a PBC, CivicaScript, that offers a subset of generics in the retail pharmacy setting (<https://civicarx.org/>)⁸¹.

Task force members concluded that an organization structure comprising a mix of different entities is most likely to advance a genetic therapy through the different stages of development, as this structure delegates responsibilities based on expertise and leverages the key advantages of each organization type (Table 2 and Fig. 2). For mixed-model organizations, well-defined governance structures are crucial to maintain public benefit goals and remain in compliance with relevant laws. Mixed-model organizations are not only feasible but are also commonly used in traditional for-profit organizations that may have affiliated foundations or non-profit organizations that engage in related philanthropic activities.

Another key component impacting CGT pricing is the availability of capital investment and the rate at which the investment is expected to be returned. With substantial upfront capital needed to develop a therapy, risks associated with high failure rates and long timeframes before revenue is generated from product sales, venture capitalists typically require a high return on investment. However, a recent analysis suggests that genetic therapies for orphan diseases and haematologic cancers that receive the green light from FDA to pursue first-in-human trials were 2 to 3.5 times more likely to obtain full approval, respectively, compared with the average drug in those areas⁸². Risk calculations should be adjusted for this increased success rate, and models that rely on capital with lower rates of return should be encouraged.

To develop a low-cost CGT, a mix of both high- and low-cost funding can be combined, with the goal of achieving a long-term stable

and moderate rate of return to investors. Although no-cost capital, such as from charitable organizations or grant funding agencies, does not require repayment, it is unlikely that an organization that is reliant solely on grant and philanthropic funding will be viable, as it would require substantial fundraising in perpetuity. Moderate-cost capital from social impact investors, venture philanthropy and social impact bonds (<https://socialfinance.org/social-impact-bonds/>) seeks to address challenges faced by people and the planet while obtaining financial returns, albeit at below-market interest rates⁸³. Other more complex financial instruments have been proposed, including a government-backed loan program to fund FDA-approved clinical trials⁸⁴, early investment by insurance companies and backstop capital, where philanthropic funding is the first money lost to reduce risk for private investors⁸⁵. Internally generated revenue can also serve as a critical source of capital to sustain an organization. This may come from royalties, offering infrastructure capacity (such as manufacturing) and expertise (intellectual and technical), tax credits, sale of a priority review voucher (Box 1) and sales of the product (Fig. 2).

With a mixed-organization model and potential funding sources in mind, we developed a hypothetical organization model (Fig. 2) that seeks to align responsibilities to governance structures and finance mechanisms. In this example, it would be critical to build mission alignment into each organization's charter to ensure continued values convergence.

What is next for CGT access

The roadmap we developed is designed to enable mission-driven entities to take CGTs from discovery to market outside of the traditional for-profit/venture capital framework in a manner that ensures maximal societal benefit. Our aim is not to replace commercial entities, and concerns have been raised that price reductions by one entity will reduce profits for all developers through competition, diminishing incentives to bring difficult-to-manufacture CGTs to market. Competition, which is typically desirable, can foster innovation and technological advances and will probably not result in a mass exodus of biotechnology companies from the CGT arena. Even at lower prices, profits to develop CGTs are still high enough to incentivize development, with our model yielding profits of US\$242 million per year in year 8 and beyond, despite being priced affordably. Existing incentives for orphan drug development extend beyond revenue from sales, and the increasing proportion of orphan drugs brought to market (Box 1) indicates capacity to absorb downward price pressures. Furthermore, our recommendations around continuing to treat ultra-rare disorders in academic settings would not require incentivizing a for-profit developer.

Inclusion of 'most-favoured nation' clauses in licensing agreements may also lead to downward price pressure, and concerns have been raised that such an approach could lead companies to increase prices in other countries to maintain profits. For drug manufactures, this approach may be challenging as many countries have already expressed an unwillingness to pay high prices for CGTs^{12,86,87}. In the EU, where governments negotiate drug prices, prices are lower for CGTs (for example, the list price of LENMELDY (atidarsagene autotemcel, Orchard Therapeutics) is £2.8 million in the United Kingdom and US\$4.25 million in United States)^{87,88}, indicating that the same company can substantially lower prices in the United States and continue to operate. Given that US taxpayers contribute substantially to R&D, healthcare costs should be fairly distributed among economic peer countries. We acknowledge that sufficiently low prices may lead to fewer products developed; however, the available products would be accessible to more individuals, including those from low- and middle-income countries, thereby benefiting more people.

We believe that the goal of achieving affordable access to CGTs is within reach. Programs such as the Made-in-Canada CAR-T program

and uses of Hospital Exemption in the European Union are evidence for the success of non-traditional manufacturing models. To support a similar model in the United States, the FDA should develop guidance for implementation of a point-of-care manufacturing model⁵¹. Globally, efforts like the Global Gene Therapy Initiative and the non-profit Caring Cross are working with local stakeholders to accomplish this mission in LMICs by building healthcare and manufacturing infrastructure and sharing intellectual property^{22,23}. The rise of social impact venture capital funds and, specifically, the recent launch of the 90-10 Institute, a non-profit organization working to establish an impact investment fund for public benefit pharmaceutical companies, demonstrate a changing landscape for financing. However, for these shifts to have the maximum impact, policy solutions are critical to advance CGT development and allow alternative models to thrive; for example, the US Congress could establish a specific IRS (Internal Revenue Service) designation for non-profit pharmaceutical manufacturing organizations to support new pharmaceutical business models like the one presented here⁸⁹. Ultimately, the field of CGT should work towards a system that allows all patients to access the benefits, regardless of disease prevalence, socioeconomic status or place of residence.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-024-07800-7>.

- Kohn, D. B., Chen, Y. Y. & Spencer, M. J. Successes and challenges in clinical gene therapy. *Gene Ther.* **30**, 738–746 (2023).
This review discusses the therapeutic potential of genetic therapies across modalities as well as key challenges.
- Vokinger, K. N., Glaus, C. E. G. & Kesselheim, A. S. Approval and therapeutic value of gene therapies in the US and Europe. *Gene Ther.* **30**, 756–760 (2023).
- Katzmann, J. L., Cupido, A. J. & Laufs, U. Gene therapy targeting PCSK9. *Metabolites* **12**, 70 (2022).
- Wu, L. L. Verve won trial success with a gene-editing milestone. Why don't investors like it? *Endpoints News* (14 November 2023).
- Sharma, A. et al. Nomenclature for cellular and genetic therapies: a need for standardization. *Transplant. Cell. Ther.* **28**, 795–801 (2022).
- Food and Drug Administration & Center for Biologics Evaluation and Research. *Cellular & Gene Therapy Products* (FDA, 2023).
- American Society of Gene and Cell Therapy & Citeline. *Gene, Cell, +RNA Therapy Landscape Report—Q1 2024 Quarterly Data Report* (ASGCT & Citeline, 2024).
- Wang, J. Y. & Doudna, J. A. CRISPR technology: a decade of genome editing is only the beginning. *Science* **379**, eadd8643 (2023).
- Allen, J. et al. Medicaid coverage practices for approved gene and cell therapies: existing barriers and proposed policy solutions. *Mol. Ther. Methods Clin. Dev.* **29**, 513–521 (2023).
This paper discusses existing challenges for state Medicaid programs to cover high-priced CGTs and proposes several policy solutions to promote equitable access.
- Witkowski, L., Norstad, M., Glynn, A. R. & Kliegman, M. Towards affordable CRISPR genomic therapies: a task force convened by the Innovative Genomics Institute. *Gene Ther.* **30**, 747–752 (2023).
This paper discusses the impetus for launching the Task Force, its structure, membership, operation and decision-making frameworks.
- Jensen, K. Orchard abandons promising gene therapy for rare immune disorder. *BioPharma Dive* (3 June 2021).
- Pagliarulo, N. Bluebird, winding down in Europe, withdraws another rare disease gene therapy. *BioPharma Dive* (21 October 2021).
- Peebles, A. Bluebird Bio sees road to revival after gene-therapy misfires. *Bloomberg* (9 June 2022).
- Vertex. Vertex and CRISPR Therapeutics announce authorization of the first CRISPR/Cas9 gene-edited therapy, CASGEVY (exagamglogene autotemcel), by the United Kingdom MHRA for the treatment of sickle cell disease and transfusion-dependent beta thalassemia. *Vertex* (16 November 2023).
- Wong, C. H. et al. The estimated annual financial impact of gene therapy in the United States. *Gene Ther.* **30**, 761–773 (2023).
- Klein, D. Cell and gene therapy logistics: meeting the supply chain challenge. *Eureka* (24 August 2022).
- Amar, D. Navigating the complexities of cell and gene therapy supply chain: a CEO's practical guide. *Forbes* (28 February 2023).
- Papathanasiou, M. M. et al. Autologous CAR T-cell therapies supply chain: challenges and opportunities? *Cancer Gene Ther.* **27**, 799–809 (2020).
- Thomson, A. M. et al. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Haematol.* **10**, e585–e599 (2023).

- Food and Drug Administration. FDA approves first gene therapies to treat patients with sickle cell disease. *FDA* (8 December 2023).
- Doxzen, K. et al. Accelerating Global Access to Gene Therapies: Case Studies from Low- and Middle-Income Countries (World Economic Forum, 2022).
- Adair, J. E. et al. Towards access for all: 1st Working Group Report for the Global Gene Therapy Initiative (GGTI). *Gene Ther.* **30**, 216–221 (2021).
- Johnson, B. Reducing the costs of blockbuster gene and cell therapies in the Global South. *Nat. Biotechnol.* **42**, 8–12 (2024).
- Vokinger, K. N., Avorn, J. & Kesselheim, A. S. Sources of innovation in gene therapies—approaches to achieving affordable prices. *N. Engl. J. Med.* **388**, 292–295 (2023).
- Mulcahy, A. W., Schwam, D. & Lovejoy, S. L. *International Prescription Drug Price Comparisons: Estimates Using 2022 Data*. Report No. RR-A788-3 (RAND Corporation, 2024).
- Becker, Z. With 2nd chance at FDA approval, BioMarin preps for hemophilia gene therapy launch in US. *Fierce Pharma* (29 June 2023).
- Lupkin, S. Feds' contract with Pfizer for Paxlovid has some surprises. *NPR* (1 February 2022).
- Cohrs, R. In new Regeneron deal for Covid drug, White House imposes price limits for first time. *STAT News* (14 September 2023).
- 117th Congress (2021–2022). H.R.5376—Inflation Reduction Act of 2022. Public Law 117-169. *Congress.gov* <https://www.congress.gov/bills/117th-congress/house-bill/5376/text> (2022).
This law includes provisions that enable the US Centers for Medicare and Medicaid Services (CMS) to negotiate prices for selected drugs with pharmaceutical manufacturers.
- Fleischut, P. M. & Haas, S. University technology transfer offices: a status report. *Biotechnol. Healthc.* **2**, 48–53 (2005).
- California Institute of Technology et al. *In the Public Interest: Nine Points to Consider in Licensing University Technology* (AUTM, 2007).
This accord highlights issues that should be considered by academic institutions to uphold shared core values when negotiating licensing agreements with private entities.
- Contreras, J. L. “In the public interest”—university technology transfer and the nine points document—an empirical assessment. *UC Irvine Law Rev.* **13**, 435–512 (2023).
This study evaluates the impacts of the Nine Points document and, given mixed adoption among signatories and little change specifically with respect to access to health-related technologies, proposes a reorientation of university policies to better align with public health and access goals.
- Menichiello, T. How creative licensing can improve patient access. *Cell and Gene* (16 November 2023).
- Mimura, C. Collaborative innovation to advance global health solutions. *Technol. Innov.* **16**, 99–105 (2014).
- Food and Drug Administration & Center for Biologics Evaluation and Research. *Guidance for Industry: Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products—Draft* (FDA, 2023).
- Kohn, D. B. et al. Autologous ex vivo lentiviral gene therapy for adenosine deaminase deficiency. *N. Engl. J. Med.* **384**, 2002–2013 (2021).
- Immune Deficiency Foundation. ADA-SCID gene therapy trials to resume in 2023. *Immune Deficiency Foundation* (13 October 2022).
- Mamcarz, E. et al. Lentiviral gene therapy combined with low-dose busulfan in infants with SCID-X1. *N. Engl. J. Med.* **380**, 1525–1534 (2019).
- Cowan, M. J. et al. Lentiviral gene therapy for artemis-deficient SCID. *N. Engl. J. Med.* **387**, 2344–2355 (2022).
- Rett Syndrome Research Trust. Rett Syndrome Genetic Medicines Summit 2023, panel discussion. *Rett Syndrome Research Trust* <https://reverse Rett.org/rett-syndrome-genetic-medicines-summit/#stack-1714423522-887-1> (2023).
- Food and Drug Administration, Center for Drug Evaluation and Research & Center for Biologics Evaluation and Research. *Guidance for Industry: Platform Technology Designation Program for Drug Development—Draft* (FDA, 2024).
- California Institute for Regenerative Medicine. *Open Manufacturing Network for Cell and Gene Therapies*. Grant No. INFR5-14719 (CIRM, 2023).
- National Institutes of Health Common Fund. Somatic Cell Genome Editing (SCGE). *NIH Common Fund* <https://commonfund.nih.gov/editing> (2024).
- Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research & Office of Regulatory Affairs. *Guidance for Industry: CGMP for Phase 1 Investigational Drugs* (FDA, 2008).
- Zu, H. & Gao, D. Non-viral vectors in gene therapy: recent development, challenges, and prospects. *AAPS J.* **23**, 78 (2021).
- Foss, D. V. et al. Peptide-mediated delivery of CRISPR enzymes for the efficient editing of primary human lymphocytes. *Nat. Biomed. Eng.* **7**, 647–660 (2023).
- Elsallab, M. & Maus, M. V. Expanding access to CAR T cell therapies through local manufacturing. *Nat. Biotechnol.* <https://doi.org/10.1038/s41587-023-01981-8> (2023).
This review discusses various models of decentralized manufacturing and outlines key opportunities, challenges and potential solutions.
- BioCanRx. BioCanRx invests \$10M in promising new cancer immunotherapy research and biomanufacturing to benefit Canadians. *Cision* (22 September 2020).
- Sánchez-Guijo, F. et al. Role of hospital exemption in Europe: position paper from the Spanish Advanced Therapy Network (TERAV). *Bone Marrow Transplant.* **58**, 727–728 (2023).
- Jayaraman, K. Cut-price CAR-T cell therapies top India's biotech agenda. *Nat. Biotechnol.* **37**, 1388–1389 (2019).
- Center for Drug Evaluation and Research. *Distributed Manufacturing and Point-of-Care Manufacturing of Drugs* (FDA, 2022).
- Moon, S., Mariat, S., Kamae, I. & Pedersen, H. B. Defining the concept of fair pricing for medicines. *Brit. Med. J.* **368**, l4726 (2020).
- National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Care Services & Committee on Ensuring Patient Access to Affordable Drug Therapies. *Making Medicines Affordable: A National Imperative*. Report No. 24946 (National Academies, 2018).

54. Novartis. *Novartis position on value-based healthcare* (Novartis, 2021).
55. Leschly, N. In pricing our gene therapy, Bluebird weighed value, shared risk, and a lifetime cap. *STAT News* (26 November 2019).
56. Yeung, K., Bloudek, L., Ding, Y. & Sullivan, S. D. Value-based pricing of US prescription drugs: estimated savings using reports from the Institute for Clinical and Economic Review. *JAMA Health Forum* **3**, e224631 (2022).
57. Richardson, M., Rind, D., Beaudoin, F. L., Pearson, S. D. & Campbell, J. D. The fair price for one-time treatments; how can we overcome existing market price distortions? *Health Affairs* (19 January 2023).
58. Hyde, R. & Dobrovolsky, D. Orphan drug pricing and payer management in the United States: are we approaching the tipping point? *Am. Health Drug Benefits* **3**, 15–23 (2010).
59. World Health Organization. *WHO Guideline on Country Pharmaceutical Pricing Policies, Second Edition* (WHO, 2020).
60. NEWDIGS FoCUS Project. *Emerging Market Solutions for Financing and Reimbursement of Durable Cell and Gene Therapies* (MIT, 2021).
61. Slocumb, T., Werner, M., Haack, T., Valluri, S. & Rader, B. *New Payment And Financing Models For Curative Regenerative Medicines* (Alliance for Regenerative Medicine, 2017).
62. PwC. Six drug pricing models have emerged to improve product access and affordability. *PwC* (23 September 2019).
63. Wouters, O. J., McKee, M. & Luyten, J. Estimated research and development investment needed to bring a new medicine to market, 2009–2018. *JAMA* **323**, 844–853 (2020).
This study analyses available data on research and development costs of over 60 therapeutics approved between 2009 and 2018 to estimate the capital needed to bring a new drug to market.
64. Vieira, M. Research synthesis: costs of pharmaceutical R&D. *Geneva Graduate Institute* www.knowledgeportal.org/_files/ugd/356854_e9d75e29c0264bf9b38118fc5f0aeab6.pdf (2020).
65. DiMasi, J. A., Grabowski, H. G. & Hansen, R. W. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J. Health Econ.* **47**, 20–33 (2016).
66. Centers for Medicare & Medicaid Services. *Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191–1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments* (CMS, 2023).
67. Pereira Chilima, T. D., Moncaubeig, F. & Farid, S. S. Estimating capital investment and facility footprint in cell therapy facilities. *Biochem. Eng. J.* **155**, 107439 (2020).
68. Spink, K. & Steinsapir, A. The long road to affordability: a cost of goods analysis for an autologous CAR-T process. *Cell. Gene Ther. Insights* **4**, 1105–1116 (2018).
69. Hodgson, V., Lemenze, M., Edwards, E. & Tomtishen, J. *Cost-Benefit Analysis of Using the Cellares Cell Shuttle Platform for Autologous CAR-T Cell Therapies* (Cellares, 2023).
70. Lee, J. Cell therapy manufacturing: build or buy? *Labcompare* (14 February 2023).
71. Kansteiner, F. Bayer, intent on its cell therapy ambitions, plots \$200M plant at overhauled Berkeley campus: report. *Fierce Pharma* (26 April 2021).
72. Ten Ham, R. M. T. et al. What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings. *Cytotherapy* **22**, 388–397 (2020).
73. Angelis, A., Polyakov, R., Wouters, O. J., Torreele, E. & McKee, M. High drug prices are not justified by industry's spending on research and development. *Brit. Med. J.* **380**, e071710 (2023).
74. Trombetta, B. 22nd annual industry audit: the pharma value picture. *Pharm. Exec.* **43**, 24–29 (2023).
75. Lopes, A., Noel, R. & Sinclair, A. Cost analysis of vein-to-vein CAR T-cell therapy: automated manufacturing and supply chain. *Cell Gene Ther. Insights* **6**, 487–510 (2020).
76. Lachaine, J., Jain, M. D., Bibeau, J., Marino, J. P. & Ball, G. PCN191 cost associated with implementation of CAR T-cell therapy for the management of hematologic cancers in Canada. *Value Health* **24**, S55 (2021).
77. Code of Federal Regulations. *Title 21, Sec. 316.31: Scope of Orphan-Drug Exclusive Approval*. 21 CFR 316.31 (CFR, 2024).
78. Suleman, F., Low, M., Moon, S. & Morgan, S. G. New business models for research and development with affordability requirements are needed to achieve fair pricing of medicines. *Brit. Med. J.* **368**, l4408 (2020).
79. Vieira, M. F., Kimmitt, R., Navarro, D., Bezruki, A. & Moon, S. in *Partnerships for Sustainability in Contemporary Global Governance* 1st edn (eds Andonova, L. B. et al.) Ch. 5 (Routledge, 2022).
80. Moon, S., Vieira, M., Alonso Ruiz, A. & Navarro, D. *New Business Models for Pharmaceutical Research and Development as a Global Public Good: Considerations for the WHO European Region* (WHO, 2022).
81. Dredge, C. & Scholtes, S. The health care utility model: a novel approach to doing business. *NEJM Catalyst* (8 July 2021).
This commentary outlines the structural and financial pillars of a healthcare utility model that can sustainably manufacture generics.
82. NEWDIGS FoCUS Project. *Are Cell and Gene Therapy programs a better bet?* (Tufts Medical Center, 2023).
83. OECD. *Social Impact Investment 2019: The Impact Imperative for Sustainable Development* (OECD, 2019).
84. 117th Congress (2021–2022). H.R.3437—LOANS for Biomedical Research Act. *Congress.gov* www.congress.gov/bills/117th-congress/house-bill/3437/text (2021).
85. Impact Entrepreneur & Rockefeller Philanthropy Advisors. *Building an Impact Economy: A Call to Action for the Philanthropy Sector* (Mission Investors, 2019).
86. Jensen, K. BioMarin secures hemophilia gene therapy coverage in Germany. *Biopharma Dive* (29 November 2023).
87. Van Kirk, A.-H. & Maltby, J. EU payment fight could cut 40% from gene therapy sales. *Bloomberg* (11 May 2023).
88. Lewin, K. Orchard sets US price tag for rare disease gene therapy Lenmeldy at \$4.25M. *Endpoints News* (20 March 2024).
89. Waxman Strategies. *Nonprofit Pharmaceutical Companies: Background, Challenges, and Policy Options* (Waxman, 2019).
This report outlines the distinct challenges non-profit pharmaceutical entities face and proposes policy solutions to promote their success.
90. Ridley, D. B., Grabowski, H. G. & Moe, J. L. Developing drugs for developing countries. *Health Aff.* **25**, 313–324 (2006).
91. United States Government Accountability Office. *Drug Development: FDA's Priority Review Voucher Programs*. Report No. GAO-20-251 (GAO, 2020).
92. Rare Disease Company Coalition. *Impact of the Priority Review Voucher Program on Rare Pediatric Disease Drug Development* (Rare Disease Company Coalition, 2024).
93. Hwang, T. J., Bourgeois, F. T., Franklin, J. M. & Kesselheim, A. S. Impact of the priority review voucher program on drug development for rare pediatric diseases. *Health Aff.* **38**, 313–319 (2019).
94. Jain, N., Hwang, T., Franklin, J. M. & Kesselheim, A. S. Association of the priority review voucher with neglected tropical disease drug and vaccine development. *JAMA* **318**, 388–389 (2017).
95. Sinha, M. S., Jain, N., Hwang, T. & Kesselheim, A. S. Expansion of the Priority Review Voucher program under the 21st Century Cures Act: implications for innovation and public health. *Am. J. Law Med.* **44**, 329–341 (2018).
96. Aerts, C., Barrenho, E., Miraldo, M. & Sicuri, E. The impact of the Priority Review Voucher on research and development for tropical diseases. *Pharm. Med.* **36**, 189–197 (2022).
97. Ridley, D. B., Ganapathy, P. & Kettler, H. E. US tropical disease Priority Review Vouchers: lessons in promoting drug development and access. *Health Aff.* **40**, 1243–1251 (2021).
98. Fermaglich, L. J. & Miller, K. L. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. *Orphanet J. Rare Dis.* **18**, 163 (2023).

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Methods

Although we primarily present key recommendations here, the impetus and context for assembling the task force¹⁰ and a comprehensive exploration of challenges and proposed solutions can be found in the full-length report⁹⁹. In brief, we assembled a multidisciplinary task force comprising 30 experts divided into four topical subgroups, covering (1) intellectual property management and licensing; (2) regulations and manufacturing; (3) pricing strategies and access; and (4) organizational and funding models. Task force contributors (Supplementary Table 1) were charged with developing a fundamentally new framework within which a genetic therapy could be taken from discovery to market. To help guide deliberations and ensure that recommendations are immediately actionable, we asked that discussions be grounded in the current regulatory landscape (as of early 2023) while recommending shifts in regulations or policy that would improve affordability and access. Task force members primarily focused on recommendations for US entities, but we also recruited non-US experts to gain international insights. While the task force often centred its deliberations around rare diseases, in alignment with the Innovative Genomics Institute's research priorities, contributors clearly recognized the need for a diversified portfolio of therapies that includes more common indications.

Data availability

No datasets were generated during the course of the study. Input data for the model was taken from cost ranges in the published literature and cited accordingly, or selected for illustrative purposes. The model can be provided on request from M.K.

99. Innovative Genomics Institute. *Making Genetic Therapies Affordable and Accessible* (IGI, 2023).

Acknowledgements We thank the members (Supplementary Table 1) of the Innovative Genomics Institute (IGI) Affordability and Accessibility Task Force, as well as the many individuals who presented to our Task Force, and particularly the patients and patient advocates for their efforts; our donors—the Doris Duke Charitable Foundation, Arnold Ventures and the Armstead-Barnhill Foundation for Sickle Cell Anemia (CureSickleCell.com); and G. Ramit for assistance with figures and graphics.

Author contributions M.K. and J.A.D. initiated the task force from which the information presented here originated. M.K. managed and chaired the task force. The following authors each chaired one of four subgroups of the task force: F.D.U. (organizational and funding models), J.H.E. (regulations and manufacturing), R.C.W. (pricing strategies/access) and S.A. (intellectual property management and licensing). M.K. and M.Z. drafted, edited and finalized the manuscript.

Competing interests J.A.D. is a co-founder of Caribou Biosciences, Editas Medicine, Scribe Therapeutics, Intellia Therapeutics and Mammoth Biosciences. She is a scientific advisory board member of Vertex Pharmaceuticals, Caribou Biosciences, Intellia Therapeutics, Scribe Therapeutics, Mammoth Biosciences, Algen Biotechnologies, Felix Biosciences, The Column Group and Inari. J.A.D. is Chief Science Advisor to Sixth Street, a Director at Johnson & Johnson, Altos and Tempus, and has research projects sponsored by Apple Tree Partners and Roche. The Regents of the University of California have patents issued and pending for CRISPR technologies on which J.A.D. is listed as an inventor. J.H.E. is a paid advisor to and receives sponsored research funding from Multiply Labs. He serves on its scientific advisory board and holds equity in the company. He is a paid advisor to and serves on the scientific advisory board of Shennon Biotechnologies and holds equity in the company. He receives sponsored research funding from Lonza, for the development of cellular therapy manufacturing devices. His research group received funding from Arsenal Bio. He is named as an inventor on patent application for CRISPR-based gene editing (WO2021183850A1). F.D.U. is a paid advisor to and holds equity in Tune Therapeutics and Cimeio Therapeutics, is a paid advisor to Ionis Pharmaceuticals, a paid consultant to Vertex Pharmaceuticals and receives salary support from DanaHER. R.C.W. is a co-founder of EditPep. The other authors declare no competing interests.

Ethical Approval: No experimentation occurred on humans or other animals. Ethical approval was not required.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41586-024-07800-7>.

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Peer review information Nature thanks the anonymous reviewers for their contribution to the peer review of this work.

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