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Preface

Nineteen genetic therapies have been approved by the U.S. Food and Drug Administration (FDA) to date, a number that now includes the first CRISPR genome editing therapy for sickle cell disease, CASGEVY (exagamglogene autotemcel). This extraordinary milestone is widely celebrated because of 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 $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 multi-disciplinary 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.

Introduction

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 United States Food and Drug Administration (FDA) are steadily increasing, with hundreds of products in development.[7] The platform nature of the underlying technologies[8], along with the ability to precisely correct specific genetic defects, now render much of the human genome 'druggable'. 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 market[11], to reach agreement on prices with payers[12] and difficulties with company viability[13] 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 indications[14] these challenges are especially acute.

A recent model simulated that 18 of 109 US-registered late-stage gene therapy clinical trials in Phase II or III will be approved between 2020-2034, costing an annual $20.4B under conservative assumptions.[15] Today, developers must contend with limited availability of critical reagents at good manufacturing practice (GMP) 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 (US) dictate who gains access to genetic therapies. As reviewed in a recent assessment of state Medicaid coverage practices in the US, gatekeeping disproportionately affects low-income Americans[9], 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 outsize 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 multi-disciplinary task force of experts and practitioners who evaluated alternative development frameworks to take genetic therapies from discovery to market.[10] The proposed solutions address intellectual property management, regulations, manufacturing technology, pricing and business models that, taken together, could reduce costs and expand access. We 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).

Negotiating access via 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 fraction of intellectual property to academia[24], meaning that, collectively, academic institutions have significant leverage. Academic technology transfer offices (TTOs) could exercise that leverage by incorporating legally binding access provisions into licensing agreements.

On average, drugs in the US are 2.78 times more expensive than in peer countries.[25] For example, the approved gene therapy Roctavian (BioMarin) has a US price of $2.9M, but in Germany the price is $1.5M.[26] As has been demonstrated recently, access provisions could institute a “most-favored nation” clause that would ensure US patients do not pay more than

patients in economic peer countries,[27,28] or could include support for particular US populations (e.g., 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.[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 which works to increase access through patent pooling and voluntary licensing.[30] 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 received,[31] these offices may be concerned that potential licensees will reject access provisions and opt to work with other universities who provide more favorable 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 Managers (AUTM).[32] 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 affordability.[33] 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 socio-economic groups, and the use of dedicated tools spreading.[34–36] 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 (e.g., guide RNA, lipids used in nanoparticles). Academic facilities that meet phase-appropriate current good manufacturing practice (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 development.[11] 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 studies.[37] This is particularly onerous for genetic therapies produced in academic cGMP facilities and tested in a small number of subjects in Phase I/II trials. For example, the transfer of manufacturing processes to commercial grade of a novel investigational *ex vivo* lentiviral therapy shown to be safe and curative in 50 subjects with adenosine deaminase deficiency (ADA-SCID: 100% overall survival ≥24 months post-treatment),[38] is estimated to cost $30M-$40M at a contract development and manufacturing organization (personal communication with Dr. Donald B. Kohn). For a disease that affects ~10 patients per year in the US and Canada, this is a tremendous financial burden of little commercial interest to for-profit biotechnology companies.[11,39]

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".[37] 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 IND; 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 significant morbidity and mortality and where early-stage clinical data show robust safety and efficacy.[38,40,41] 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 changes to the purification method of a lentivirus used to transduce stem cells *ex vivo* to carry less risk than similar process changes for an AAV intended to be administered systemically and lessen comparability requirements accordingly.

Innovative solutions

Designating well-characterized manufacturing processes as platforms would be particularly helpful in mitigating the cost and labor intensity of current regulatory requirements. The leadership of FDA's Center for Biologics Evaluation and Research (CBER) has enunciated a vision for leveraging the platform nature of genetic therapies by using nonclinical information between 'parental' and 'offshoot' products that differ only in one component (e.g., the guide RNA).[42] 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. 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 Medicine (CIRM).[43] Government programs such as the Bespoke Gene

Therapy Consortium[44] and the Platform Vector Gene Therapy (PaVe-GT) pilot[45] are important contributions towards achieving this goal.

Academic centers 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 ~100% of the subjects in several studies experiencing resolution of major disease symptoms.[1,38,40,41] 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 Investigational New Drug (IND)"). Early-phase requirements are deemed by the FDA sufficient to allow studies in human subjects, with adequate informed consent, monitoring, and adverse event reporting in place.[46] In the case of CGTs, close follow-up of subjects 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.[47,48]

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 cryopreservation.[49] In the point-of-care model (a type of distributed manufacturing), a treating hospital or local cGMP facility produces the cell therapy product which allows for rapid

administration of the modified cells in patients.[49] Closed, automated manufacturing plays 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 - which produces cell therapies at a tenfold lower cost than the commercial option - is a prime example of the impacts a distributed manufacturing model with government backing can have on affordability and access.[50–52] While point of care manufacturing, through mechanisms such as a local "hospital exemption", is lowering prices in other countries,[23,53,54] this is near impossible to implement in the US without changes to the current regulatory framework.[49,55]

The price is wrong

The most obvious question is: Why are the prices for CGTs so high? Secondly, what is a reasonable price to ensure that life-saving therapies continue to be developed while not overburdening payers, patients and the healthcare system?[56]

For-profit companies have a fiduciary responsibility to maximize shareholder value, and the high prices of CGT 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.[57–59] 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 society.[60] 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 others.[61] Most importantly, value-based prices are not set in relation to the cost of development and production.[10] 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 payers. Even with a pricing framework that prioritizes affordability, insurance coverage will be necessary. Insurers in the US will cover treatments between $50,000 and $250,000 without additional scrutiny or coverage limitations.[62]

We evaluated several pricing philosophies (e.g., cost-plus, portfolio-based approaches) as well as payment models (e.g., subscription, outcomes-based pricing, healthcare loans).[63–66] 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 of a new drug between $314M and $2.8B (with a cost of capital between 7% and 11%, including failures).[67–69] An analysis of 63 drugs approved by the FDA between 2009 and 2018 found a median cost of capitalized R&D of $1.14B (including failures).[67] In the model presented in Table 1 we estimate $1B for drug development costs as sufficient to account for investment in failed projects and used an estimated 8% cost of capital— this figure is used by CMS in its implementation of the 2022 Inflation Reduction Act to determine whether a for-profit brand-name drug manufacturer has recouped drug development costs.[70]

The cost to build and adequately equip a manufacturing plant that can produce autologous therapies ranges from several million to hundreds of millions USD in the published literature, with variability dependent on the facilities' size, location and project-specific factors.[71–74] The upfront construction and equipment costs of a facility with the capacity to produce 500 to 5,000 batches per year was estimated at $200M for the model,[73,75], a figure confirmed as a reasonable

estimate by the combined expertise of task force members with many years of experience in manufacturing cell and gene therapies (Table S1). Operating costs for a cell therapy were estimated to be between $8,000 to $23,000 per patient,[73,76] extrapolated to 2,000 patients per year, this is a fixed production cost of $16M to $46M. Selling, general and administrative costs can be significant, and the 15 largest biopharmaceutical companies spend more on these activities than R&D,[77] ranging from 24.5% to 51.9% of revenue in 2022.[78] This model (Table 1) estimates $75M 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 $60,000 to $90,000 per dose.[24,79,80] 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, FDA guarantees an exclusivity period of 7 years, meaning it will not approve another product for the same indication with the same active moiety.[81]

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 $2B for drug development, the price would increase by 26% to $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 $1B to develop would require a per-patient price of $1.68M. If the drug was administered to 10,000 patients per year, its price would drop to $132,699 per patient. Organizationally, this underlines the importance of a diverse portfolio of

products, where profits from therapies with larger patient populations can be used to subsidize the cost of bespoke therapies for ultra-rare diseases.

While there is uncertainty in the cost to build and operate a cell and gene therapy facility,[71–74] these values have a smaller impact on prices than the number of patients. If the manufacturing facility costs $4M the estimated sustainable price would be $241,064 while at the higher end of the reported range at $861M, the cost per patient would be $317,270. The time horizon over which development costs are recovered and profits calculated can be extended. In this model any profits generated after the initial 7 year period ($242M 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). Since 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 essential.[82] We reviewed organization types including 501(c)(3) charitable organizations, 501(c)(4) social welfare organizations, medical research organizations (MROs), public benefit corporations, and mixed models of multiple aligned organization types with governance structures that ensure mission alignment (Table 2).

The most common alternative business model of pharmaceutical R&D are public-private product development partnerships, which have successfully launched over 50 products to the market over the last two decades for neglected diseases like tuberculosis, malaria and cholera.[83] In these

arrangements a nonprofit 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 approaches.[84] Among organizations that the task force engaged, those employing mixed models were more common, these included Medicines360, a nonprofit MRO that distributes and commercializes products globally through an LLC subsidiary, ImpactRH360, and in the US through the for-profit CuraePharma.[85] Furthermore, Civica Rx, a 501(c)(4), has successfully tackled generics shortages through a healthcare utility model, and has established a philanthropic arm (Civica Foundation, 501(c)(3)) as well as a public benefit corporation, CivicaScript, that offers a subset of generics in the retail pharmacy setting.[86,87]

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, 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 also commonly used in traditional for-profit organizations that may have affiliated foundations or nonprofits 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 significant 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 hematologic 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 to the average drug in those areas.[88] Risk calculations should be adjusted for this increased success rate, and models that rely on capital with lower rates of return 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. While no-cost capital – such as from charitable organizations or grant funding agencies – does not require repayment, it is unlikely that an organization 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 seeks to address challenges faced by people and the planet while obtaining financial returns, albeit at below-market interest rates.[89,90] Other more complex financial instruments have been proposed, including a government-backed loan program to fund FDA-approved clinical trials,[91] early investment by insurance companies, and backstop capital, where philanthropic funding is the first money lost to reduce risk for private investors.[92] Internally generated revenue can also serve as a critical source of capital to sustain an organization. This may come from royalties, offering infrastructure capacity (e.g., 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's 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 way 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 cell and gene therapies to market. Competition, which is typically desirable, can foster innovation and technological advances and will likely not result in a mass exodus of biotechnology companies from the CGT arena. Even at lower prices, profits to develop CGTs are still significant enough to incentivize development, with our model yielding profits of $242M 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-favored 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.[12,93,94] In the EU, where governments negotiate drug prices, prices are lower for CGTs (e.g., the list price of LENMELDY is £2.8M in the UK and $4.25M in US),[94,95] indicating that the same company can significantly lower prices in the US 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 the Hospital Exemption rule in the European Union are evidence for the success of non-traditional manufacturing models. To support a similar model in the US, the FDA should develop guidance for implementation of a point-of-care manufacturing model.[55] Globally, efforts like the Global Gene Therapy Initiative and the nonprofit 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 nonprofit working to establish an impact investment fund for public benefit pharmaceutical companies, demonstrate a changing landscape for financing. However, for these shifts to have 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 designation for nonprofit pharmaceutical manufacturing organizations to support new pharmaceutical business models like the one presented here.[96] Ultimately, the field of cell and gene therapy should work towards a system that allows all patients to reap the benefits, regardless of disease prevalence, socioeconomic status or place of residence.

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Figure Legends

Figure 1: Key Stakeholders and Challenges in Genetic Therapy Development. A CGT 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 investigational new drug application (IND)-enabling studies and, in a number of cases, Phase I/II trials. They are typically funded by government and philanthropic grants which 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 $25M 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 done '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 (i.e., center of excellence). This medical center helps patients navigate insurance coverage, orders the drug product, and oversees staff training. Patients may spend months at the center 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.

Figure 2: Hypothetical alternative organization employing 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 IP 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 ultimately 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 are distinct from those commonly found in academia. In the US, 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, generating revenue by offering manufacturing capacity to commercial partners. While being separate legal entities, the organizations could have overlapping board of directors who would assure that coordination is a top priority. In this example, the MRO (a nonprofit) controls the IP and can make decisions on priorities that are not purely profit driven.

Box 1. Priority Review Voucher

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 diseases,[97] and has since been extended to rare pediatric diseases.[98] Upon 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 four 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 $350M.[98] In recent years, the valuation of PRVs appears to have stabilized, with vouchers for rare pediatric diseases sold between $95M and $111M in the 2020-2022 period.[99] Vouchers play a role in business decisions, with one nonprofit company relying entirely on profits from the sale of its PRV.[98] In 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.[100–103] The future of the program is uncertain, given mixed reports of their incentivizing effects, increasing supply (and therefore reduced value) and strain on FDA staff to manage the

program and accelerate reviews.[98,100,101,104] Congress could let the PRV program for rare pediatric diseases lapse if it chooses not to reauthorize it by the end of September 2024. Importantly, 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 in the 2001-2005 period to 48% during 2016-2020, thanks to tax breaks, fee reductions and longer market exclusivities, among other incentives.[77,105]

Methods

While we primarily present key recommendations here, the impetus and context for assembling the task force are detailed in Witkowsky and Norstad *et al*., 2023.[1] A comprehensive exploration of challenges and proposed solutions can be found in the full-length report.[2] Briefly, we assembled a multi-disciplinary 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 (SI 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 centered 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 Statement

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 upon request from melinda.kliegman@berkeley.edu.

Methods References

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Author Contributions

MK and JD initiated the task force where the information presented in the manuscript originated. MK managed and chaired the task force. The following authors each chaired one of four sub-groups of the task force: FDU-organizational and funding models, JHE-regulations and manufacturing, RW-pricing strategies/access and SA-intellectual property management and licensing. MK and MZ drafted, edited and finalized the manuscript.

Competing Interests

Jennifer Doudna 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. Doudna 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 Jennifer Doudna is an inventor.

Jonathan H. Esensten is a paid advisor to and receives sponsored research funding from Multiply Labs, Inc. 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, Inc. 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).

Fyodor D. Urnov 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 Corporation.

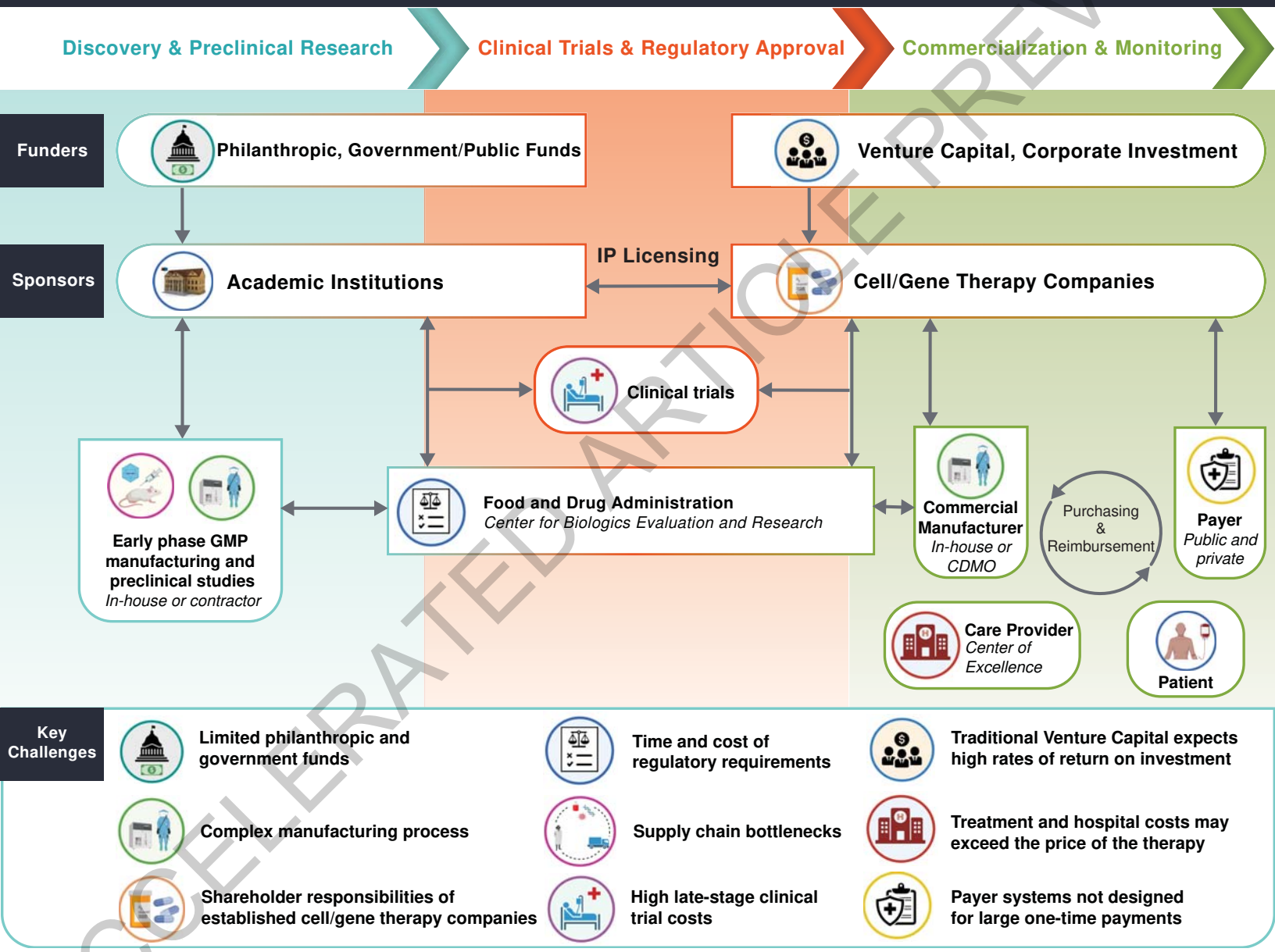
Ross Wilson is a co-founder of EditPep, Inc.

Melinda Kliegman, Susan Abrahamson, and Manar Zaghlula have no competing interests to disclose.

Additional Information

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

Key Stakeholders and Challenges in Genetic Therapy Development



Proposed Organizational Model

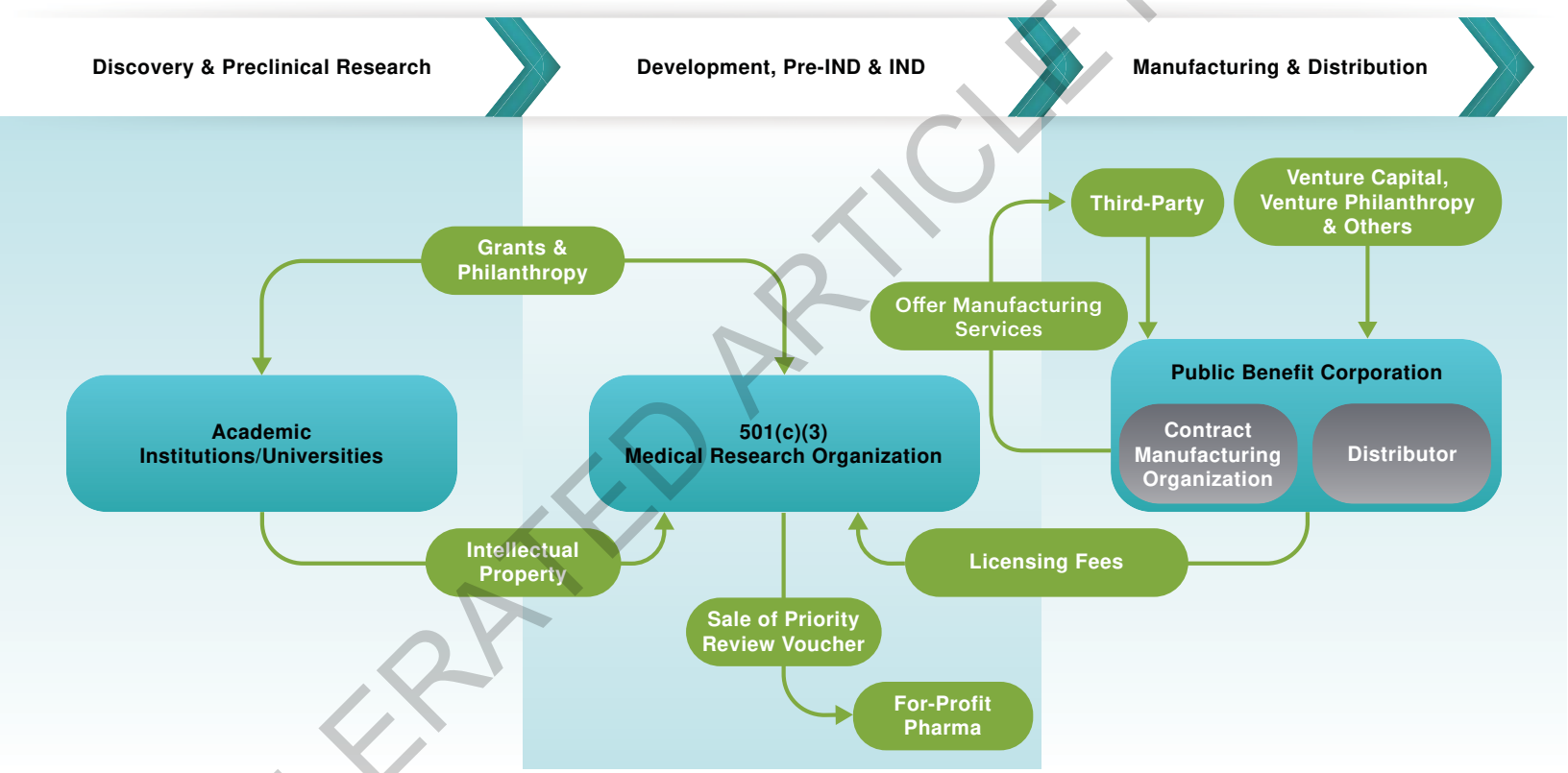


Table 1 The 10× less model

Item	Assumption	Calculation	Cost per Patient
Number of Patients per year	2000		
Time Horizon to Recover R&D Costs	7 years		
Manufacturing Costs per patient	$100,000		$100,000
Annual Fixed Production & Marketing	$75 million	Divide annual costs by number of patients per year	$37,500
Manufacturing Plant Construction	$200 million	Divide one-time fixed cost by number of patients over time horizon	$14,290
R&D Costs to Recover	$1 billion	Divide R&D costs by number of patients over time horizon	$71,430
Cost of Capital	8 percent	Divide average annual cost of capital by number of patients over time horizon	$20,993
Net Profit	$200 million	Divide net profit by number of patients over time horizon	$14,290
Estimated Sustainable Price			$258,500

Table 1 Legend: A hypothetical organization wishes to treat an average of 2,000 patients per year within seven years on the market, the Orphan Drug Exclusivity period granted by FDA for rare disease therapies. In this example, manufacturing costs of the therapy are assumed to be $100,000 per treatment. Annual fixed costs of operations and marketing (including physician education) are $75M and there is a one-time fixed cost of building and equipping a manufacturing plant of $200M. The organization wishes to recover R&D costs of $1B at an 8% cost of capital. At this cost of capital, $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 $1.2B (R&D costs of $1B plus the manufacturing plant of $200M). A $200M profit is also included. Spreading costs across 2,000 patients per year for seven years brings the sustainable price of the therapy to $258,500 per patient. If a priority review voucher (PRV) is awarded, it could be sold for roughly $110M; however, since this is not a guarantee, we chose not to include it in this example.

Table 2 Key Considerations for Alternative Business Models

Organization Type	Advantages	Disadvantages
Nonprofit Organization 501(c)(3) Medical Research Organization 501(c)(4) Social Welfare Organization	• Mission Focus • Tax-Exempt • Grant & philanthropically funded • Greater public trust	• Difficult raising funding • Ineligible for business funding programs • Challenges compensating talent • Limits on commercial sales • MROs only; active research required
Public Benefit Corporation	• 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	• Significantly lowers costs to (public) healthcare systems • Stable, low-cost financing • Government coordination on clinical development and regulations	• Substantial infrastructure investment • Administrative/ logistical complexities • Country-specific

Table 2 Key Considerations for Alternative Business Models: Opportunities and challenges for nonprofit entities, public benefit corporations (PBCs), government-backed initiatives, and mixing of models.