



**MAKING  
GENETIC THERAPIES  
AFFORDABLE AND  
ACCESSIBLE**

# ABOUT THE INNOVATIVE GENOMICS INSTITUTE

[The Innovative Genomics Institute \(IGI\)](#), founded by Nobel Laureate Dr. Jennifer Doudna in 2017, is a public, academic research organization formed through a partnership among multiple University of California campuses, the Lawrence Livermore National Laboratory, and Gladstone Institutes.

The IGI brings together scientists and innovators from diverse disciplines to unlock the potential of CRISPR technology to solve some of humanity's greatest challenges. IGI researchers innovate in biomedicine, agriculture, climate science, and genome engineering. The institute is working toward a world in which genomic technologies are deployed in an ethical, socially responsible, and equitable manner.

The impacts of genome-editing technologies reach far beyond the laboratory. Hence, the IGI has a dedicated [Public Impact Program](#). Led by Dr. Melinda Kliegman, the Public Impact team strives to understand the social, ethical, and legal implications of this rapidly advancing field of science through research and drives informed policymaking and public discourse by engaging key stakeholders and the public.

## Acknowledgements

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# FOREWORD



Research universities play a foundational role in scientific discovery and technological innovation, exemplified by the incredible trajectory of genomic technologies. In under a decade, CRISPR tools have evolved from an experimental possibility to a clinical reality. Now we are at an inflection point; treatments targeting diseases that impact millions of lives are in development, with some in late stage clinical trials. While the therapeutic potential of genetic therapies is immense, their real-world impact will be limited if we do not secure access for everyone who stands to benefit.

I receive emails weekly from parents around the world who are hopeful that CRISPR will lead to a different outcome for their children. Making CRISPR cures broadly accessible was incorporated as a core component of the Innovative Genomics Institute's mission, which aims "to bridge revolutionary genome-editing tool development to affordable and accessible solutions in human health". CRISPR's ease of use makes it particularly well-suited for rare genetic diseases, for which less than 10% have an approved treatment option. While the private sector is essential for bringing effective therapies to market, standard business models do not incentivize the commercialization of therapies with a small market share (despite successful policies to encourage drug development for rare diseases). This is a gap that I believe academic institutions are well-positioned to fill.

As part of the nation's top public university system, the IGI takes seriously its commitment to accessibility. To this end, the institute's Public Impact program, led by Melinda Kliegman, was established to align innovation with societal values and facilitate equitable access to breakthrough therapies. This mandate is built upon the idea that research institutions are not only where discoveries are made, but where the sustainable translation of novel therapies into health systems can be catalyzed. Achieving this ambitious goal requires deconstruction and critical analysis of the current gene therapy development pipeline and a reimagination of discovery through care delivery.

The learnings of this Affordability Task Force provide alternative models for the success of genetic therapies. The goal is to share creative suggestions with a growing community of innovators eager to change the status quo. I am grateful for the contributions from this esteemed group of experts with first-hand experience confronting limitations within current drug development pipelines, and who possess the sectoral diversity necessary to create a level of change that will sustainably move gene therapies from benchtops to bedsides.

I am confident we can reach a point where genome editing reaches all who would benefit most. Health systems should help us realize the possibility of a cure rather than create financial barriers. Given the rapid acceleration of genome editing technology, now is the time to innovate access so all could enjoy its benefits.

*Jennifer Doudna*

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# EXECUTIVE SUMMARY

We have arrived at a new frontier in medicine. Cell and gene therapies hold the promise of targeted treatments - potentially even cures - for an array of devastating and life-altering diseases. While innovation in biomedicine continues, many novel therapies may never reach patients despite the existence of clinic-validated components. To accelerate affordability and access to genetic therapies in the United States and globally, we assembled a Task Force to delineate the challenges but also concretize opportunities and alternative avenues that can make high-cost therapies affordable, and move new therapies from bench to bedside.

This report is the conclusion of a yearlong deliberation by 30 individuals with expertise spanning from preclinical development of genetic therapies to healthcare economics, intellectual property rights, and biomanufacturing, with the goal of identifying concrete steps to make genetic therapies affordable and accessible. Genetic therapies hold the potential of transformational health outcomes, yet at prices surpassing \$3M, affordability and access are of significant concern to patients and payers alike. We evaluated alternative approaches to developing and deploying a genetic therapy that would reach more patients. We discussed how a non-traditional entity would be organized and financed and how it might price a genetic therapy. We also scoped manufacturing efficiencies and identified strategies for intellectual property (IP) and pricing.

The three decade history of cell and gene therapy shows that academic institutions are the primary originators of novel therapeutic strategies and typically accept government and philanthropic grants to conduct research, generating significant intellectual property. In turn this IP is licensed to for-profit organizations who further develop the product. This model belies a contradiction for academic institutions; while most have a public benefit mission, which supports making final products generated with university IP affordable and accessible, they generate valuable income from licensing intellectual property and are reasonably concerned about requirements that would deter licensees. We believe that changes to intellectual property licensing practices are one of the easiest/first changes that academic institutions can take to promote access. We propose that academic institutions should impose reasonable requirements in licenses that ensure access to life-saving therapies. Some recommendations include explicitly supporting academic technology transfer offices (TTOs) in activities to improve affordability and access, consideration of non-exclusive licenses particularly in low- and middle-income countries, and the development of access plans that identify how the product will reach patients without private insurance or facing other barriers to access.

With regard to organizational models that can operate in parallel to publicly traded, for-profit companies, Task Force members first evaluated existing, non-traditional, pharmaceutical entities. They determined a mixed organizational model comprising an academic institution, a nonprofit medical research organization (MRO), and a public benefit corporation (PBC) could be an ideal structure. The MRO would accept funding from grants and private philanthropy to conduct research, it could concentrate intellectual property, conduct clinical trials, and generate further income by selling priority review vouchers from FDA approvals. Subsequently, the MRO could license core



# EXECUTIVE SUMMARY

technology to a PBC, which could price a drug based on the cost of goods and labor to manufacture, plus some surplus to ensure sustainability. For example, a PBC could manage manufacturing, distribution, and negotiations with payers. The PBC would also be charged with fundraising and expanding sources of revenue by working with socially-oriented VC firms and seeking early investment from payers or offering services.

Lastly, we would like to acknowledge that manufacturing a genetic therapy to stringent regulatory standards is a key driver of cost. While entities currently developing therapies need to comply with existing regulations, the FDA has shown an impetus to update regulatory requirements to make products more accessible. In particular, we expect that increased regulatory support for point-of-care manufacturing models would drive down prices and allow greater geographic access while not reducing the safety or efficacy of the treatments. We provide examples where other governments, who have supported point-of-care manufacturing models, have increased affordability.

In the year since we initiated this report several companies have decided to either delay or discontinue further development of genetic therapies in their pipeline, some for explicit business reasons. From our analysis, it seems that in addition to challenging manufacturing and delivery mechanisms, the need to generate enough capital to recoup investments is confounding. We present concrete actions that academic institutions and downstream stakeholders can take to address these issues, allowing more therapies to enter the market and thereby improve access through competition.

Each section in this report begins with an executive summary and recommendations for that section, then delves into background on the topic followed by a conclusion. We also include a section on actionable policy recommendations and provide illustrative examples of an implementation strategy at the end.

A challenge of this magnitude requires a wide range of stakeholders to implement innovative solutions while, for the sake of equity, not seeking maximum profit. We hope this report builds a robust foundation for these and similar solutions to take hold.

# 1. INTRODUCTION

In 2017, the United States (US) [Food and Drug Administration \(FDA\)](#) approved the first cell and gene therapies – Kymriah and Luxturna. Since then, new [genetic therapy](#) candidates (e.g., gene addition therapy, oligonucleotide therapy, and genome-editing approaches) have proliferated, with several receiving FDA approval.<sup>1</sup> Notably, as of May 2023, market prices of these interventions, some with curative potential, are surpassing \$3M ([Table 1](#)). Such price tags pose financial challenges for both patients and [payers](#). Given the profound health impacts these emerging therapies may have, affordability has become a matter of health equity.

For decades, new drugs have followed a similar pathway to market: governments and philanthropies fund basic science and early-stage research, which is then licensed to for-profit companies who invest the capital to further develop and test drugs in clinical trials and shepherd them through regulatory approvals. Prices are then set by the company - with a view to recouping its investments, paying for other candidate product failures, and meeting investor and shareholder expectations - and, once launched onto the US market, coverage and reimbursement is determined by payers based on regulatory assessments of safety and efficacy.

Cell and gene therapies face challenges at multiple steps in the pathway to market. First, some target ultra-rare<sup>F1</sup> indications, like Strimvelis (approved by the European Medicines Agency), which is used to treat infants born with ADA-SCID, a severe immunodeficiency. Given the very small patient population (an estimated 15 patients per year in

Europe<sup>3</sup> and 10 patients per year in the US and Canada<sup>4</sup>), the traditional pharmaceutical model based on manufacturing scale and efficiency is ill-equipped to develop and launch these therapies. Furthermore, the costs of manufacturing to regulatory compliance, including those of expensive materials like clinical-grade plasmid DNA contribute to exorbitantly high-priced therapeutics.

Innovators and venture capitalists move forward with products based on assessments of potential revenues, costs, risks, and uncertainty. In some instances, therapies are abandoned because forecasted volume and price cannot sustain commercial viability. For example, Orchard Therapeutics abandoned their promising gene therapy for ADA-SCID because there was “no viable path forward” according to CEO Bobby Gaspar.<sup>5</sup> We argue that the inaccessibility of cell and gene therapies is not a failure of individual pharmaceutical companies, but rather, a system-wide deficiency. Innovative models are urgently needed to properly serve patients.

To assess possible solutions to affordability and access issues, the Innovative Genomics Institute (IGI), an academic partnership among multiple University of California campuses, assembled an Affordability Task Force led by the IGI’s Public Impact team. This group comprised 30 experts ranging from physicians and researchers, health economists, intellectual property experts, and biopharmaceutical manufacturers from the US, Canada, Brazil, and Europe, with the goal of identifying concrete steps toward affordable and accessible genetic therapies.

<sup>F1</sup> The term ultra-rare is not well-defined and there is no specific patient number threshold that differentiates a rare from an ultra-rare disease. The N-Lorem Foundation<sup>2</sup>, for example, uses N=1-30 patients worldwide as a cutoff for providing ASO therapies, citing the near-insurmountable challenges of showing safety and efficacy in such a small patient population in a commercial setting.

## Task Force structure

The Task Force was arranged into four subgroups that each addressed one of four areas critical to affordability and access (Figure 1). The subgroups conducted their work through monthly meetings, literature reviews, interviews, and discussions. The full Task Force convened monthly to share progress and discuss complementarity of proposed solutions. IGI personnel were embedded in each subgroup to ensure proposed solutions were implementable and to maintain continuity across the Task Force.

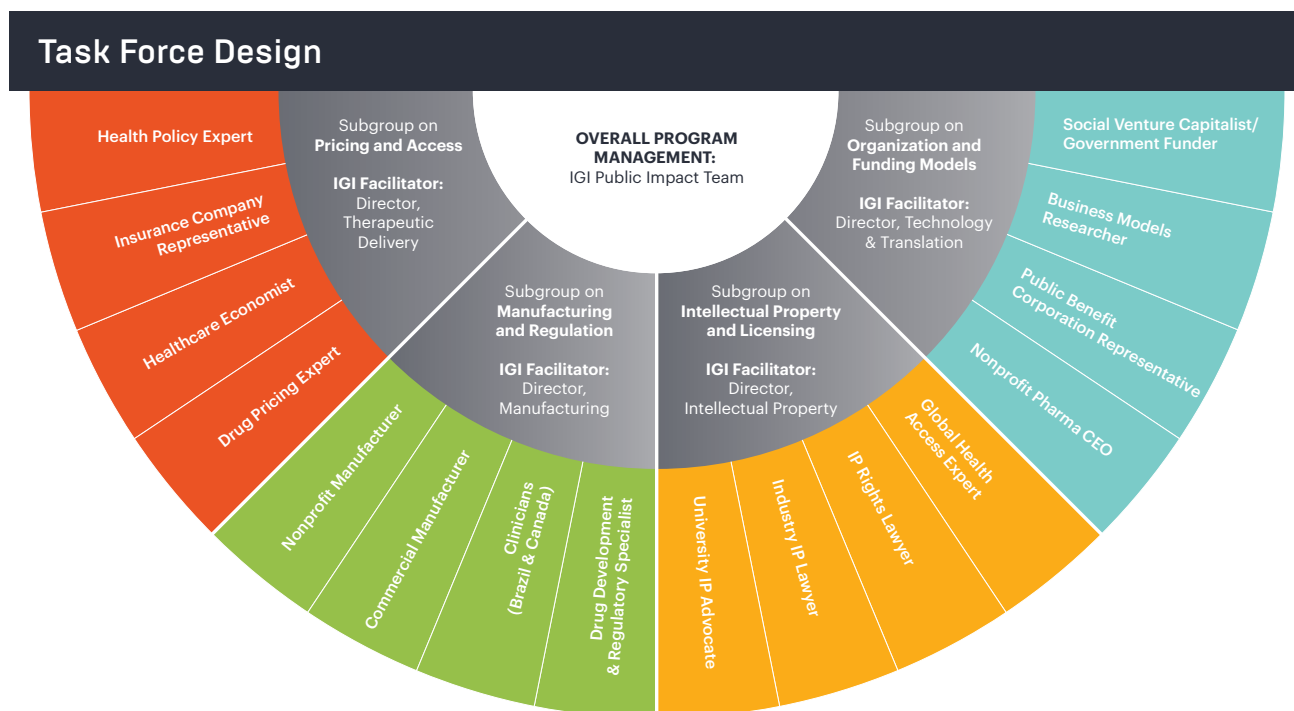


Figure 1: Task Force Design

## Scope

The overall goal was to develop an alternative framework that can operate in parallel with the traditional for-profit/venture capital model and offers a sustainable approach that ensures therapies - even for the rarest of diseases - can be produced and delivered equitably to patients in need. To help guide deliberations and discussions, we set several scope-defining parameters from the outset. First we define what an equitable, affordable and accessible therapeutic would entail in [3. Pricing and Access](#).

To generate concrete and actionable recommendations, we framed our discussions around existing policies and regulations (as

of 2023). We recognize that the regulatory framework for cell and gene therapies is evolving and that many legislative and policy efforts are underway with the goal of lowering drug prices. Importantly, we considered recommendations out of scope if they necessitated prior substantive regulatory changes or new legal provisions to be viable. In contrast, policy recommendations that would facilitate operations, or those that would help with implementation of existing measures (e.g., licensing agreements with robust access provisions for low- and middle-income countries) were considered in-scope. While most of our Task Force participants are US-based

and our primary focus is on implementable recommendations for US entities, we recruited Task Force members from several other countries to highlight international perspectives.

We discussed several innovations in process and technological advances in the field, such as [in vivo delivery](#) of genetic therapies, that would lower the cost of administration. While technological advances are an important piece of the puzzle, by themselves, they will do little to expand access globally. Without innovation in organizational models, intellectual property provisions, pricing strategies, funding and payment mechanisms, and other policies, any savings derived from biotechnological improvements may not be reflected in list prices, ultimately impacting access. To ground discussions, we limited our scope to therapies within IGI's development pipeline (e.g., we did not examine oligonucleotide therapies or oncolytic viral therapies). Nonetheless, we believe many of the recommendations presented are generalizable across high-cost therapies.

The subgroup on Intellectual Property narrowed its scope to actionable steps that can be taken by [academic institutions](#), as the generators of intellectual property, to enhance affordability of and access to genetic therapies globally. They consulted with expert practitioners in the field to vet their recommendations.

Task Force deliberations often centered on [rare diseases](#) in alignment with IGI research priorities. However, it quickly became apparent that a diverse product portfolio, including therapies for diseases with larger patient populations, is needed to offset the costs of research and development (R&D), manufacturing, and distribution of commercially inviable therapies.

Lastly, it was crucial that we comprehensively assess the challenges at each of the various stages of R&D, manufacturing, and commercialization, and that we consider out-of-the-box, multi-pronged solutions even if they have not been tried and tested yet.

## 2. BACKGROUND: THE PHARMACEUTICAL ECOSYSTEM

While there is no single approach for translating basic research, there is a generalized pathway with key players (Figure 2). A typical genetic therapy originates in an academic institution and culminates in patient dosing. Here we provide an overview of the interactions among these players, but expand on them in greater detail throughout the report.

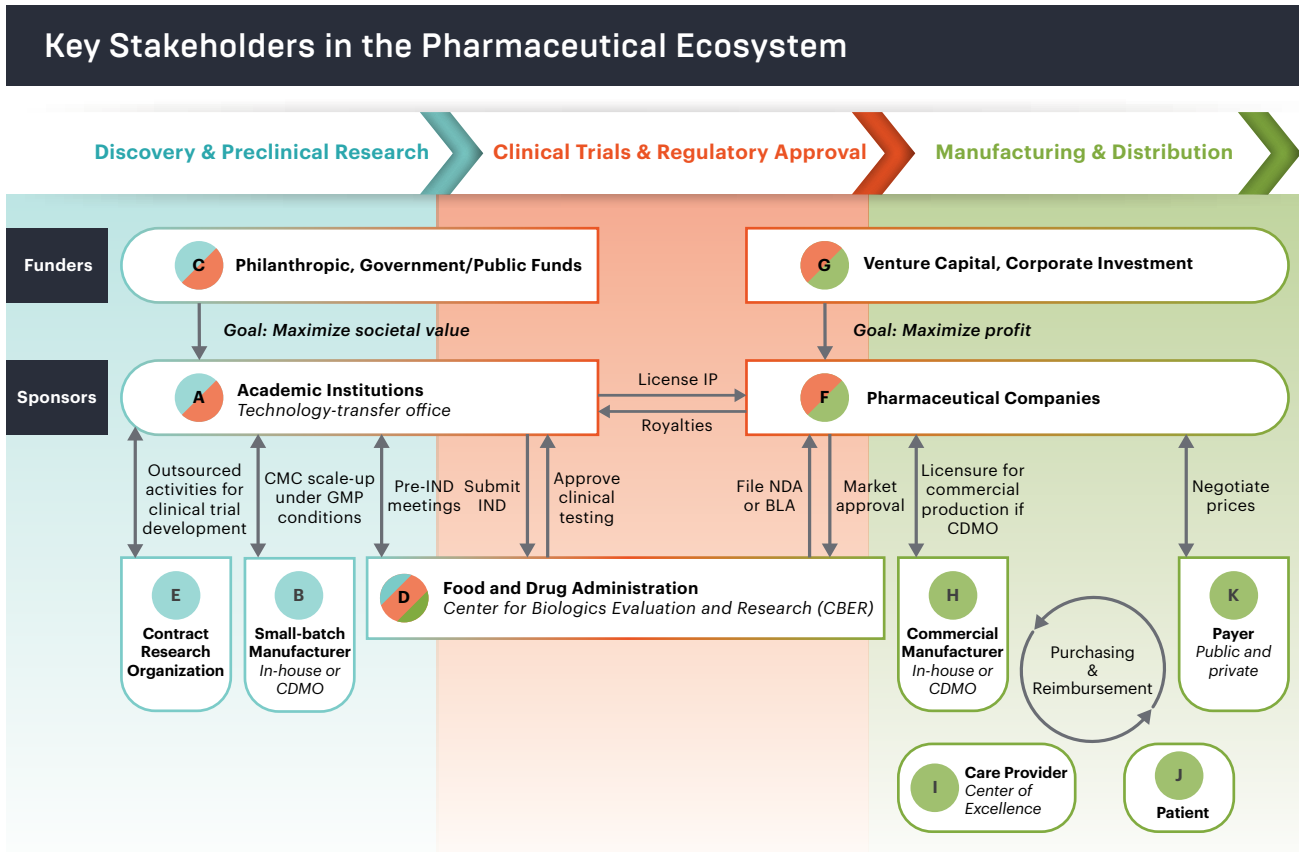


Figure 2: The Key Stakeholders and Interactions Involved in Bringing a Genetic Therapy from Conception to Patients

### Discovery and early-stage clinical testing

[Academic institutions](#) (Figure 2, **A**) have driven a majority of cell and gene therapy clinical development [programs](#) and are well-positioned to drive initial drug discovery efforts through [Investigational New Drug \(IND\)](#) enabling studies, and finally Phase I/II trials. Given the extensive expertise present in academia, bringing together a multidisciplinary academic team capable of clinical studies has the potential to accelerate drug product development. Each entity of the academic team can be recruited from existing

faculty and labs; however, assembling a project team de novo in industry is more challenging because each entity must be recruited, and expertise for a specific disease is often underdeveloped. Pre-clinical and early-stage clinical testing only require small batches of biologics, and academic [Good Manufacturing Practice \(GMP\)](#) facilities (**B**) can generally meet that demand ([4. Manufacturing and Regulation](#)). An academic team should also have expertise in the targeted disorder, including pharmacology and toxicology, and experience in conducting Phase I/II clinical trials.

This approach typically relies upon a combination of [public and philanthropic funding](#) (C) to sustain the effort, something academic teams are accustomed to raising. A barrier for academic teams as they move from discovery research to preclinical and eventually Phase I trials is a lack of regulatory knowledge and experience necessary to engage the [Food and Drug Administration \(FDA\)](#) (D), specifically the Center for Biologics Evaluation and Research, and navigate IND submissions. It is typical to incorporate a consultant or a [Contract Research Organization \(CRO\)](#) (E) into the team to ensure that IND-enabling datasets around efficacy, safety testing, and manufacturing are built appropriately. If the target indication is a rare pediatric disease and the FDA approves the therapy, the FDA could award the trial [sponsor](#) with a [priority review voucher](#), which can be used by the same sponsor or sold to another for expedited review in the future. Vouchers for rare pediatric diseases have been worth between \$95M and \$111M between 2020 and 2022.<sup>6</sup>

### Late-stage testing and regulatory approval

While academic teams may have the capacity to conduct Phase I/II clinical trials, the infrastructure and resources necessary for late-stage clinical testing (Phase III) often require engagement with a pharmaceutical company (F). [Technology-transfer offices](#) (A) within academic institutions connect academia and industry by [licensing](#) patent rights to companies to commercialize products. Intellectual property can be licensed to startups, backed by venture capital investors (G), or to larger pharmaceutical companies (often publicly-traded), both of which are financially incentivized to maximize profits.

Once Phase III trials are completed, drug sponsors may file for a [Biologics License Application \(BLA\)](#), which allows them to market the product if approved. To move from Phase I/II to Phase III trials and eventual broad distribution requires significant scale-up. Commercial-scale manufacturing can be

done 'in-house' by large pharmaceutical companies or contracted to a [Contract Development and Manufacturing Organization \(CDMOs\)](#) (H). CDMOs can reduce costs by centralizing expertise and infrastructure, precluding the need for pharmaceutical companies to invest in manufacturing infrastructure or pay recurring maintenance and personnel costs.

### Distribution

Sponsors of a novel, FDA-approved [genetic therapy](#) typically engage the medical centers that supported the clinical trial(s) for commercial delivery. Sponsors usually create a treatment team under the auspices of a [care provider](#) (i.e., [center of excellence \(COE\)](#) or quality treatment center (QTC) (I). This genetic therapy center helps patients navigate insurance coverage, orders the drug product, and oversees training of staff and other medical team members. The center usually maintains long-term follow up after treatment, and is able to meet any post-market regulatory requirements.

Patients may spend months at the medical center during multi-step treatments. Considering many [patients and families](#) (J) reside far from the COE, social services are a key component for delivering the therapy and these may include housing, transportation and day-to-day costs during these extended stays. COE's report these are a significant patient unmet need and charitable advocacy groups are being called upon to financially assist in lowering such barriers.

Broadly speaking, in the US healthcare ecosystem healthcare insurance premiums, cost sharing, and medical claims are paid by individuals and organizations including health plan providers, employers, health maintenance organizations, public entities such as government organizations (Medicare or Medicaid), and patients (K). In this report we define [payers](#) more narrowly as public and private insurers responsible for paying healthcare medical claims, such as hospital stays, procedures, and therapies.

## Select Genetic Therapies in Development

Name	Manufacturer	Target Indication	Stage of Development List Price	Clinical Trial Number	Estimated US Patient Population (Prevalence + 2-5 Years Incidence) * Unless otherwise noted
Adstiladrin	Ferring Pharmaceuticals A/S	Non-muscle invasive bladder cancer	Approved		<a href="#">60,000 adult patients</a>
Hemgenix	CSL Behring LLC	Hemophilia B	Approved \$3.5M in the US		2,600 adult patients
Luxturna	Spark Therapeutics	Inherited retinal dystrophy	Approved \$425K per eye in the US		1,000-2,000 adult & pediatric patients
Skysona	Bluebird Bio	Cerebral adrenoleukodystrophy	Approved \$3M in the US		700 pediatric patients
Vyjuvek	Krystal Biotech, Inc.	Dystrophic epidermolysis bullosa	Approved \$631,000 per year		900 patients
Zolgensma	Novartis	Spinal muscular atrophy	Approved \$2.125M in the US		11,000 patients
Zynteglo	Bluebird Bio	Transfusion-dependent beta thalassemia	Approved \$2.8M in the US		1,450 adult & pediatric patients
Libmeldy	Orchard Therapeutics	Metachromatic leukodystrophy	Approved (EU, UK) £2.8M in the UK Phase III (US)	NCT04283227	400-1,700 pediatric patients worldwide
Roctavian	BioMarin Pharmaceutical	Hemophilia A	Approved (EU) -€1.5M in the EU Phase III (US)	NCT03370913	7,500 adult patients
Strimvelis	Orchard Therapeutics	Adenosine deaminase severe combined immunodeficiency	Approved (EU, UK) €594K in the EU		15 infants annually in Europe 10 infants annually in US and Canada
Upstaza	PTC Therapeutics	Aromatic L-amino acid decarboxylase deficiency	Approved (EU, UK) £3M in the UK Phase II (US)	NCT04903288	100 pediatric patients worldwide
CRISPR_SCD001	UCSF Benioff/UCLA/Innovative Genomics Institute	Sickle cell disease	IND approved	NCT04774536	58,000 adult & pediatric patients
GS030	GenSight Biologics	Retinitis pigmentosa	Phase I/II	NCT03326336	65,000 adult patients
Rexin-G	Epeius Biotechnologies	Pancreatic cancer	Phase II	NCT00504998	62,000 patients annually
Collategene	AnGes	Critical limb ischemia	Phase II	NCT04267640	2.3 million adult patients
CTX001	CRISPR Therapeutics/Vertex Pharmaceuticals	Sickle cell disease	Phase II/III	NCT03745287	58,000 adult & pediatric patients
dabocemagene autotoficel	Castle Creek Biosciences	Recessive dystrophic epidermolysis bullosa	Phase III	NCT04213261	400 adult & pediatric patients
delandistrogene moxeparvovec	Sarepta Therapeutics	Duchenne muscular dystrophy	Phase III	NCT05096221	4,000 pediatric patients
RGX314	RegenxBio/Abbvie	Neovascular age-related macular degeneration	Phase III	NCT04704921	2 million adult patients
Engensis	Helixmith	Painful diabetic peripheral neuropathy	Phase III	NCT04469270	7.1-13.5 million adult patients

Table 1. Select genetic therapies showing the broad range of patient population sizes as well as list prices for approved products exceeding \$3M.

## 3. PRICING AND ACCESS

What factors determine the cost and price associated with a [genetic therapy](#)?

Pharmaceutical companies typically price new drugs based on a profit motive, driven by fiduciary responsibility to shareholders. Although generating profits undoubtedly contributes to the high prices of genetic therapies, there are other considerations that impact pricing, such as: complex manufacturing processes, clinical trial costs, technology licensing fees, hospital treatment costs, the need to recoup investments associated with research and development (R&D), and the value these therapies provide to patients. Prices may be high even without being inflated to ensure profitability, and many companies justify the high price of genetic therapies with the potential value these therapies provide to patients and health systems.

We first evaluate current pricing frameworks and the key drivers of price and then ask what an alternative pricing strategy might look like. Next, we put forward an alternative model that is grounded in the cost to produce a therapy.

### Scope

Before we assess the factors which influence the price and delivery of genetic therapies, we must first define what an affordable and accessible price means in this context. A genetic therapy is affordable if clinically eligible patients will not be denied or forced to forgo treatment based on insurance type and coverage status, a prevalent issue in the US complicated by the variety of [payers](#) and insurance plan designs. Most patients rely on insurance (public or private) to cover costly medical treatments. This implies that for a treatment to be priced affordably, insurers must provide genetic therapy coverage to clinically eligible patients without excessive coverage

limitations that render treatment inaccessible. A recent study highlights the reality that several state Medicaid programs and Medicaid Managed Care Organizations impose restrictions more stringent than the FDA-approved label, leading to delays or denials that can severely impact patient outcomes or make previously eligible patients ineligible.<sup>7</sup>

For this report, we consider \$250,000 (in 2023 US dollars) to be an affordable, accessible target for genetic therapy drug product list price; this figure was referred to by insurers as needing little extra justification or measures in order to provide coverage. However, price targets may adjust based on the therapeutic benefits and costs associated with specific treatments and patient population size. For uninsured patients, making genetic therapies accessible necessitates programs and resources to assist with costs in addition to outreach advocates who can help individuals navigate and access these financial resources.

Affordability is a necessary but insufficient condition for access. We define access comprehensively to include the support systems that will help patients receive genetic therapy treatment and help them and their families respond with resilience. The cost to administer the treatment in a hospital setting could be more than the cost of the therapy itself due to long hospital stays. Additional support systems are also needed to assist with travel, lost time from work for patient and caregiver, navigation of health systems and insurance, social services, active care management, and after care. Even when treatments and associated services are mostly covered by insurance or a national health system, patients are sensitive to out-of-pocket costs. Research has found that patients who face



cost sharing that is not covered by insurance consume less necessary medications - including insulin for the management of diabetes and immunosuppressive medications to prevent rejection of solid organ transplants.<sup>8</sup>

Additionally, high costs exacerbate existing inequities in health care.<sup>9</sup> This is even more so for genetic disorders that disproportionately impact certain races and ethnicities. In 2021, non-white individuals were more likely to be uninsured with American Indian/Alaskan Native and Hispanic having the highest rates of uninsured persons at 21.2% and 19.0%, respectively (KFF, 2022).<sup>10</sup> To date in the US, we have only limited experience with genetic therapies in the clinical setting, but for cancer - which often requires expensive, targeted treatments - younger, lower-income individuals with public health insurance were most likely to go into debt or file for bankruptcy after a cancer diagnosis.<sup>11</sup> The forthcoming genetic therapies to treat sickle cell disease<sup>12,13</sup> are likely to bring the issue of health inequity to the forefront, given that the patient population is primarily of African descent.<sup>14</sup> Health disparities in access to pharmacological interventions are already stark<sup>15</sup>, so it is imperative that we work diligently to not exacerbate or extend these disparities with genetic therapies.

### Recommendations

An affordable, accessible genetic therapy begins with the patient in mind. We envision a system in which manufacturers work with public and private insurers, [care providers](#), and patient advocacy groups to integrate support for patients and their caregivers from diagnosis through treatment and beyond. A key component is developing incentive schemes to bring about such changes to price calculation and profit margin assessment. For an entity focused on delivering therapies at an affordable and accessible price we recommend the following:

- Consider alternative philosophies to value-based pricing; the dominant approach used by those currently developing genetic therapies
- Strongly link the price of the product to the cost of developing and deploying the drug. We propose an alternative pricing strategy, which we term a 'dynamic cost-plus approach'
- Set profit margins that ensure long-term sustainability of the entity

We recognize that there are inherent challenges in the current system that have served as roadblocks to consistently delivering equally affordable and accessible care which we address in the pages that follow.

### Pricing in the pharmaceutical industry

Below we outline several key factors that impact how therapies are typically priced in the pharmaceutical industry.

#### Patient population

The size of a clinically defined patient population directly affects the overall demand for a given therapy. Factors such as the number of doses needed per patient and the duration of treatment dictate how companies estimate revenue and determine whether they can take advantage of economies of scale. This interplay between how therapies are administered and their short- and long-term demand can be used to justify high prices.

Many genetic therapies target [rare and ultra-rare disorders](#), and this means that for most genetic therapies there is a limited pool of patients from which to recoup development costs. A drug's orphan status can be used as a proxy for aggregate demand and is associated with high costs at launch.<sup>16</sup> Additionally, genetic therapies are often delivered as a single dose, curative treatment and therefore do not provide an ongoing stream of revenues for companies to recoup costs over time.

### The cost of development and delivery

Drug companies frequently cite large investments in R&D and the need to recoup costs of failed trials as a justification for high drug prices. Widely cited studies estimate the capitalized R&D cost per product to develop a new drug to be anywhere from \$314M to \$2.8B (including failures)<sup>17-20</sup> with the cost of capital between 7% and 11%.<sup>17,21</sup> During the first 10 to 12 years of drug development, a company invests tens or even hundreds of millions of dollars each year. If the drug is approved by the [Food and Drug Administration \(FDA\)](#), it will likely generate a stream of revenues over a period of at least 12 to 15 years or until generic or biosimilar competition takes place. While ranges in the hundreds of millions to billions of dollars are undoubtedly large figures, it is difficult to determine whether investments in drug development are directly linked to price. One recent study evaluated investor reports to obtain information on spending and found no correlation between list/net price and spending on R&D of 60 new therapeutics approved by the FDA in the past decade.<sup>16</sup> Though primarily focused on the largest drug companies, reflecting pharmaceutical drugs, additional analyses reveals that it is more common for profits to be distributed to shareholders than reinvested in R&D.<sup>16,22,23</sup>

### Value justification

Another approach that has gained popularity and endorsements from the National Academies of Science, Engineering and Medicine and the American Medical Association, among others, is value-based pricing. This method bases the price of a drug on the magnitude of its benefits to patients, the healthcare system, and society. The healthcare system in the US is made up of multiple and distinct entities that need value justifications to carry and deliver these therapies. These entities include hospital

pharmacies, providers, insurance companies (payers), and patients.

In the US, the nonprofit Institute for Clinical and Economic Review (ICER) provides an independent, third-party review to evaluate the value of a therapy using data on efficacy provided by companies. Several other high-income countries have similar organizations such as the National Institute for Health and Care Excellence in the United Kingdom and the German Federal Joint Committee, though these institutions have a much greater ability to influence prices and national formularies compared with ICER. Value-based pricing uses a marginal analytic framework of incremental benefits versus costs relative to other treatment options, with the goal of rewarding innovation that brings benefit.<sup>24</sup> ICER analyzes the cost-effectiveness of different treatment options by comparing health benefits, gains in length of life, and economic cost for the entire patient population. The quality-adjusted life year (QALY) and equal value of life years gained (evLYG) are standards for conducting cost-effectiveness analyses that considers the extension of life and improvement in the quality of life to evaluate treatments.<sup>25,26</sup> Typically, \$50,000 to \$150,000 is used as a cost-per-QALY threshold in the US.<sup>27,28</sup>

Insurers in the United States (US) will generally cover treatments between \$50,000 and \$250,000 without additional scrutiny or coverage limitations.<sup>29</sup> For genetic therapies that are potentially curative over a lifetime and negate future health care costs, value assessments of greater than \$1M are common. Recent ICER estimates of \$2.9M as a fair price for Hemgenix, a gene therapy for hemophilia, illustrate the limits of a value-based pricing approach in promoting affordability and health equity.<sup>14,30</sup> Additionally, publications by ICER acknowledge that value-based pricing may inadvertently build

in expensive standard-of-care costs into the value of a new therapy and proposes that cost savings could be shared equally between the health system and manufacturer, or instituting an annual cost-offset cap of returns to the manufacturer.<sup>31</sup> It is notable that the cost of administration and post-treatment monitoring of cell and gene therapies in a hospital setting may be far greater than the cost of drug product manufacturing. In an analysis by Prime Therapeutics, the costs of administering a CAR-T therapy beyond manufacture were found to accrue to nearly \$1M.<sup>32</sup>

### Alternative pricing philosophies

We evaluated alternative pricing philosophies aimed at lowering costs by tethering the final price of the product to the cost to develop and deliver the drug. We also discussed how to ensure maximum insurance coverage and thus deliver the lowest cost to patients. Alternative pricing philosophies included cost-plus models, portfolio-based approaches, and contract-based approaches such as outcomes-based pricing. In discussing maximizing insurance coverage, we evaluated the subscription insurance model and spoke to multiple individuals working in Medicaid administration. One assumption inherent to any alternative pricing structure is that the entity providing the drug would need to be self-sustaining.

Simple cost-plus models, in which one calculates the [cost of goods](#) and labor plus some predetermined profit margin, are one approach that has been discussed in the literature and that is still used in some [low- and middle-income countries \(LMICs\)](#). This model has recently been popularized by financier Mark Cuban, who launched his own Cost Plus Drug

Company as a way to offer low-cost generic prescription drugs ([Box 6](#)). While this works well for generics that people can afford to purchase out-of-pocket, it is not a feasible model for high-cost genetic therapies.

Through economies of scale, the more patients treated with a particular therapy, the lower the price will be. If the ultimate motive is to provide access and affordability while ensuring the organization continues to operate, excess revenue could be used to subsidize the development costs for commercially non-viable therapies, such as those for ultra-rare disorders. Thus the entity would look at sustainability across the entire portfolio of products rather than on a product-by-product basis to determine viability<sup>F2</sup>.

Outcomes-based pricing/rebates is a type of contract approach that links specific predetermined health metrics to payments made to the manufacturer in installments over time. This approach attempts to share the risk between the manufacturer and the insurer for therapies without a [real world evidence](#) of durability and efficacy. While outcomes-based approaches work in theory, the insurers we spoke to indicated that they were difficult to implement as they require keeping track of many drug manufacturers and patient outcomes over time. To help address this issue for public payers, the US Department of Health and Human Services is testing the Cell and Gene Therapy Access Model pilot, under which the Centers for Medicare and Medicaid Services (CMS) would administer multi-state, outcomes-based agreements with biopharmaceutical manufacturers.<sup>35</sup>

<sup>F2</sup> To help developers, the World Health Organization has developed a tool<sup>34</sup> to model funding needs across a portfolio of health products.

### A 10x less price: the dynamic cost-plus approach

The model presented below combines several pricing philosophies to develop what we are calling a dynamic cost-plus approach. Consider an alternative pricing framework that might be adopted by a public benefit or nonprofit company ([6. Organization and Funding Models](#))

that develops and markets cell and gene therapies. Such a company could set a price while holding the following goals in tension:

- Maximize clinically appropriate access
- Prioritize affordability for patients and the healthcare system
- Recover the costs of drug development
- Sustain the organization and support future drug development

#### Illustration of an alternative pricing framework

Task Force members considered an illustrative example of the factors that a nonprofit company might consider as it sets a price for a cell or gene therapy that would generate a revenue stream high enough to recover drug development costs ([Table 2](#)). This illustrative example is based on estimates of development or manufacturing costs within the range of values in the published literature.

Suppose that the organization wishes to recover R&D costs of \$1B within seven years on the market, the [Orphan Drug](#) Exclusivity period granted by FDA for rare disease therapies ([Table 1](#)). In this example, manufacturing costs of the therapy are assumed to be \$100,000 per treatment – for illustrative purposes. Annual fixed costs of operations and marketing (including physician education) are \$75M and there is a one-time fixed cost of building a manufacturing plant of \$200M. The final feature

of this sustainable pricing model is to consider the cost of capital. For for-profit companies, that cost is typically the rate of return required by the company's investors to fund the project. For riskier projects the cost of capital may be higher. The cost of capital is lower in a nonprofit setting as investors may be willing to accept a lower rate of return, all else equal, compared to shareholders of a for-profit company. This may occur, for example, if investors in the nonprofit company also value the benefits its success would provide to society at large or if some funding comprises low or no-cost government or philanthropic funding as discussed further in [6. Organization and Funding Models](#). Still, projects with a higher risk should have a higher cost of capital, even in a nonprofit setting.

The pricing model presented here is grounded in the literature that compares the capitalized costs of R&D to the present discounted value of the returns to R&D. Estimates of the capitalized costs of R&D account for risk in two ways. First, these estimates account for investment in drug candidates that fail during the development process. Second, the cost of capital is incorporated into the estimate which can also account for risk. Our assumption of \$1B for drug development costs is high enough to account for the cost of capital as well as investment in failed projects since many of these therapeutic programs are high risk.

To reasonably account for the cost of capital in our illustrative example, we sought guidance from CMS in its implementation of the 2022 Inflation Reduction Act<sup>36</sup>. CMS decided to use a cost of capital of just over 8% when determining whether a for-profit brand-name drug manufacturer has recouped its drug development costs.<sup>37</sup> For this illustrative example we therefore also use a cost of

<sup>F3</sup> If a priority review voucher (PRV) is also awarded, it could be sold for roughly \$100M; however, since this is not a guarantee, we chose not to include it in this example.

capital of 8%. At capitalized costs of R&D and the manufacturing plant of \$200M, spreading these costs across 2,000 patients per year over seven years brings the sustainable price of the therapy to almost \$244,000 per patient. At this price, the net present value of the profit stream generated over the seven-year period will equal \$1.2B.

### **Sensitivity analysis**

The framework can be modified to recover any specified level of drug development costs. For example, if the funds that the company seeks to recover for drug development were to double to \$2B, the price in this example would increase by 36% to \$333,000 per patient.

Pricing under this framework is extremely sensitive to the number of patients expected to receive the therapy each year. For example, a treatment for an ultra-rare disease affecting 200 people per year that cost \$1B to develop would require a per-patient price of \$1.5M. If the drug was administered to 10,000 patients per year, its price in this example would drop to \$129,000 per patient.

It cannot be emphasized enough that this framework is simply illustrative and is intended to show how R&D costs and the size of the annual patient base affect the price that a nonprofit might charge with a sustainability goal in mind. The sensitivity of the price to the time horizon over which development costs are to be recovered can also be explored.

This framework does not account for many uncertainties in the market that put upward pressure on the price in order to be sustainable over time. For example, the number of patients that can be expected to take the drug is very difficult to predict. Uptake by patients is uncertain as is the number of competing therapies that FDA may approve over the seven year time horizon.

This framework is primarily intended as a starting point for others in the field to consider how a nonprofit entity might price a brand-name cell or gene therapy if the goal is to increase access with an eye toward affordability and sustainability over time.

The 10X 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	\$100,000		\$100,000
Annual Fixed Production/Marketing Costs	\$75 million	Divide Annual Costs by Number of patients per year	\$37,500
Manufacturing Plant Construction	\$200 million	Divide one time fixed costs by number of patients over time horizon (14,000)	\$14,290
Cost of Capital	8 percent		
R&D Costs to Recover	\$1.2 billion	Divide R&D costs by number of patients over time horizon	\$85,710
ESTIMATED SUSTAINABLE PRICE			\$244,000

Table 2. The 10X Less Model - An illustrative example of how an alternative pricing framework could dramatically lower the price of a genetic therapy while recouping R&D costs over the orphan drug exclusivity period.

### Reimbursement and coverage strategies

Even with a pricing framework that prioritizes affordability, insurance coverage will be necessary to translate affordability beyond the health system and to the patient. While the pipeline of high-cost therapies, particularly in the cell and gene therapy space, has been limited to date, in 2023 alone more than 20 new therapies are expected to come to market, with several likely to have multi-million dollar price tags upon approval. For payers and their members, these price tags present challenges to financial solvency. Coverage could be in the form of a bundled payment to hospitals for both the therapy and the cost of service delivery or as a stand-alone for the therapy itself. The specific approach will depend on the hospital’s ability to make a sustainable margin while delivering care. It is important to note that the coverage scenario will vary between public and private payers.

Government payers mandate price discounts and an entity seeking to provide affordable therapies can take advantage of two government programs: the 340B Drug Rebate Program and Medicaid.<sup>38</sup>

The 340B program makes price discounts available to all safety-net providers whether nonprofit or private. This program allows safety-net providers to purchase certain outpatient drugs at discount prices. Currently gene therapy is not administered in an outpatient setting.

Medicaid plans are administered at the state level, and a demonstration or pilot program with one state could show positive, long-term benefits that would be attractive for other states. The Cell and Gene Therapy Access Model pilot announced by HHS to administer multi-state agreements could accelerate integration of gene therapies by Medicaid plans.<sup>35</sup>

Private payers, such as health plans, self-funded employers, or other entities responsible for the cost of the health benefits of their enrollees - and who thus also bear the financial risk for providing coverage - will generally cover the majority of the cost of a high-cost therapy, in accordance with members' benefits and associated cost sharing, including potential coverage limitations and prior authorization. Coverage of a therapy is typically also based on clinical review by an independent panel of physicians who evaluate efficacy and provide guidance on coverage criteria.

In the case of a health plan insurer, covering the majority cost of these therapies has the potential to erode mandatory risk-based capital requirements, and lead to raised premiums to offset cost impacts. For an employer, the cost to cover and administer a single therapy may prove overly burdensome without risk protection programs in place (e.g., stop loss, reinsurance). For member patients, even at a lower cost share, the price of a genetic therapy may prove untenable without the support of patient financial assistance programs.

Given this, there is growing consideration for solutions to mitigate the risk of the impact of these high-cost therapies. Alternative approaches, such as risk protection solutions, specifically targeting high-cost therapies are likely to garner greater attention as the number of these therapies coming to market proliferates. These approaches include: outcomes-based arrangements, reverse pricing, pooling, and warranty models. These solutions will seek to limit some of the financial impact to payers and, by extension, may in part help to reduce the risk of potential larger insurance premiums increases to their members.

### **Paying for expensive therapies**

As a note, while how to pay for expensive therapies is outside this Task Force's scope,

we would like to acknowledge that several strategies have been proposed elsewhere.<sup>39-41</sup> A key hurdle to access is the expectation that multi-million dollar price tags must be covered in a single, upfront payment. One model proposes the use of health care loans equivalent to home mortgages that are paid over a longer time period while the benefits are reaped throughout.<sup>42</sup> However, insurance switching, common in the US, would make this model difficult to implement. Another model is a subscription-type payment structure in which insurers pay a small monthly premium to gain access to all high-cost therapies in the event one of their members needs them.<sup>43</sup> With a sufficiently large member base, this model can spread the costs incurred by any individual, incentivize insurers to identify all patients in need of a therapy, and potentially bring down costs as drug manufacturers secure a reliable source of cash flow. As more high-cost genetic therapies are approved, payers and policy makers will have to test and optimize which payment models work best.

Regardless of reimbursement and payment strategies, if an organization ([6. Organization and Funding Models](#)) were to enter the market with a lower-cost genetic therapy, it would create market competition, putting downward pressure on prices of for-profit pharma companies producing genetic therapies that treat the same condition. As long as the new drug product has a different chemical moiety or mechanism of action, it would not trigger exclusivity provisions granted by FDA. Since the nonprofit would be charging a price that accounts for its costs of drug development, those lower prices would still reward innovation but also help to enable many genetic therapies (not just those marketed by the nonprofit) more affordable for patients and the healthcare system.

### Conclusion

There are many different ways that an organization delivering a genetic therapy may choose to price their products; we provide one potential approach. Our Task Force recommends that, in order to assure affordability, the price of the product should be closely linked to the cost of development and manufacturing. Preferably, an organization will evaluate its required profit margins to ensure long-term sustainability and price products accordingly. This margin needs to consider the costs to scale and maintain the current therapy, sustain company overhead, meet the access mission goals for patient affordability and include a margin for future treatments. Given the need to temper profit maximization, it is unlikely that an entity considering this approach will be a traditional for-profit organization and we discuss alternative organizational structures in [6. Organization and Funding Models](#).

Any entity seeking an affordability-driven approach to pricing should also consider innovative payment arrangements. Examples include soliciting early investments from payers to scale manufacturing in exchange for future price guarantees or bundling hospital services (which can be higher than the manufacturing cost) with the cost of the drug product to bring down the overall costs, particularly for 340B covered entities who offer free care to patients. Developing new pricing arrangements will be an iterative process of negotiating among the manufacturer, payers, and COE/hospitals. We believe that a product priced using this approach can be up to 10 times less costly than existing products on the market while still ensuring the organization can continue producing the drug product.



## 4. MANUFACTURING AND REGULATION

Development and manufacturing of cell and gene therapies can take many years and cost hundreds of millions of dollars. The costs are highly variable depending on the product, prevalence of the disease, and the level of rigor required in the regulatory filing. In many cases, the development of a drug begins in an academic setting and is transferred to a commercial company due to the resources required to move beyond Phase I trials. However, there is a risk that a promising drug product could stall in commercial development due to business considerations or other issues unrelated to safety and efficacy.

Manufacturing capacity for newly-developed cell and gene therapies is limited by the small number of lower-cost academic cGMP laboratories (i.e., those compliant with [current Good Manufacturing Practice](#) regulation) and the high price of [contract manufacturing organizations \(CMOs\)](#). In addition, wait times for specific products such as viral vectors can be months or years at commercial CMOs. Building and maintaining the cGMP-compliant facilities needed to manufacture products even for early phase trials as well as developing quality assurance and quality control programs are very expensive. Academic investigators and small biotech companies often struggle to raise the capital and identify the appropriate partners for manufacturing.

### Scope

The goal of this subgroup is to outline the pre-clinical and clinical stages and estimate cost of product development for [genetic therapies](#). We focus on key manufacturing and regulatory factors that influence cost and highlight several funding mechanisms that can be leveraged to support product development in an academic setting. We also explore innovative manufacturing models,

such as platform technologies and distributed point-of-care manufacturing, and consider international perspectives.

### Recommendations

In order to address the challenges in manufacturing, we recommend the following:

- Develop standardized platform technologies, including detailed standard operating procedures and an inexpensive license, to simplify and speed the development of new cell and gene therapies. For example, a guide RNA/nuclease combination that is well characterized and available for commercial and non-commercial knock-in of genes. An established platform that regulatory authorities know and trust would greatly decrease the time and funding required to develop the drug manufacturing process.
- Focus on technology that will enable closed, automated, standardized processes for distributed manufacturing. Open manufacturing processes in ISO7-classified clean rooms are expensive and not scalable. Especially for analytic assays where validation and standardization are critical from an early phase, there is an urgent need for automated solutions. [Funders](#) should commit resources given the high-cost nature of technology development.
- Develop non-viral methods for gene modification. Viral vectors are a major obstacle to rapid and cost-effective development of new drug products. CRISPR-based solutions with shorter manufacturing lead times and lower [costs of goods](#) are therefore critical to the advancement of the field. At the same time, availability of GMP-grade DNA products (e.g., single-stranded DNA, nano-plasmids) will become

increasingly rate-limiting and an expansion of manufacturing capacity is needed to meet the demand of these technological advances.

We note that these recommendations require a level of protocol sharing, data sharing, and [non-exclusive licensing](#) of intellectual property that is currently rare in the field. Leadership in this area from nonprofits and academic institutions is critical to providing resources for both academic and industry players. Innovation in manufacturing and flexible regulatory frameworks can be greatly enabling to the field and allow more patients to access affordable therapies in a timely manner.

### Drug development process

Broadly, the development process for cell and gene therapies can be divided into four stages: 1) discovery through pre-[Investigational New Drug \(IND\)](#), 2) pre-IND through IND submission, 3) Phase I/II clinical trials, and 4) Phase III trials through BLA. We provide a description of a typical drug discovery process in greater detail in [Table 3](#).

### Discovery through pre-IND

The proof-of-concept studies, pre-clinical studies, and process and analytical development are often grant-funded, and only the essential studies that will confirm the scientific validity of an approach are performed. These studies provide proof of principle that the therapeutic approach may have disease modifying activity. A series of related therapeutic candidates may be compared for efficacy and initial signs of toxicity in vitro in cell lines or in primary patient cells, and in vivo in appropriate, available animal models. A final therapeutic candidate should be selected at this stage and advanced through additional studies.

At this time, a regulatory guidance meeting, such as a FDA INTERACT (Initial Targeted Engagement

for [Regulatory Advice on CBER Products](#)), may be requested to present the findings to date and obtain feedback on proposed subsequent pharmacology and toxicology studies, as well as preliminary plans for drug CMC and broad outlines of a Phase I clinical trial. Feedback from regulatory authorities at this early stage is important to guide the subsequent set of studies. More defined studies of the drug activity, pharmacology, and pilot toxicology are performed. The drug manufacturing process is finalized by producing one to three batches of cell product to obtain data on the process's reproducibility/robustness and the expected product characteristics. When promising preclinical data is observed, the university and principal investigator frequently engage an industry partner to advance product development.

### Pre-IND through IND submission

Data from the above studies are used to support a pre-IND meeting with the FDA where plans for IND-enabling pharmacology, toxicology, the manufacturing approach ([Chemistry, Manufacturing, and Controls, or CMC](#) studies), and the clinical trial design are discussed. Following these plans – with modifications based on the regulatory guidance– the definitive pharmacology and toxicology studies, and CMC engineering or qualification runs are performed under GMP conditions.

Major aspects of the Phase I trial, including patient characteristics (number of patients, inclusion/exclusion criteria), treatment plan, monitoring for safety and efficacy, and stopping rules, is determined and may undergo local regulatory review (e.g., Institutional Review Board, Scientific Review Committee). The [sponsor](#) of the new drug product submits a complete IND application that is reviewed within

30 days and either approved or placed on hold pending additional requested information or changes. Once the IND is accepted and the Institutional Review Board grants approval, the clinical trial may begin.<sup>44</sup>

### Phase I/II clinical trials

First-in-human, early-phase clinical studies are frequently performed in an academic setting. Typically, drugs go through successive phases of clinical trials, with Phase I representing first-in-human studies mainly focused on safety and possibly determining a maximum tolerated dose. If the Phase I trial shows an acceptable safety profile, researchers may initiate Phase II studies which often use dosing information from the Phase I trial, and are designed to identify a therapeutic efficacy signal. However, for rare, orphan disorders, these stages are sometimes combined into a Phase I/II trial with endpoints for both safety and efficacy and a definitive pivotal study meant to obtain sufficient data to support a New Drug Application (NDA) or BLA for marketing approval. During clinical trials for [autologous](#) drug products, sufficient CMC process characterization data must be gathered concurrently with drug product manufacturing.

### Phase III trials through BLA

Phase III trials are often large, randomized against a standard of care, and seek to obtain definitive evidence of efficacy; these are typically funded by industry partners. During the initial engagement with an academic institution, the industry partner aims to identify data gaps and estimate the bridging effort from prior clinical trials. A lack of infrastructure and experienced staff on the academic side complicates this initial gap analysis and may interfere with the transfer to a commercializable setting. Despite promising clinical data from academic GMP facilities, industry partners will face new regulatory and quality requirements when moving from Phase

I through to Phase III trials. This will include manufacturing process characterization, and rigorous assay validation that may impede or even prevent the industry partner from gaining marketing approval.

In the case of [rare diseases](#), approval may require data from every lot produced. If these data are not collected from the earliest clinical stages, the industry partner may not be able to progress with product development. Hence, this creates tension between the desire of academic groups to move quickly and perform scientifically sound proof-of-concept trials, and industry partners who take on such projects with a goal of commercialization.

Following completion of Phases I–III, the drug sponsor may apply for a [Biologics License Application \(BLA\)](#), which encompasses all of the cumulative clinical safety and efficacy data, the CMC drug product batch analysis results and outlines the planned clinical drug manufacturing plan and strategy for process control for the licensed drug. The approval of the BLA by the FDA allows the drug to be marketed and sold in the United States. The price of the drug product is not a consideration in the FDA approval process, and insurers are required to pay for FDA-approved drugs for [patients](#) when deemed medically necessary. Outside of the US, national health authorities may deny payment for drugs if the cost-to-benefit is not favorable.

### Estimating cost of development

The costs for development and manufacture of cell and gene therapy products are variable with few hard numbers available in the literature. Estimates based on expert or consultant opinion indicate that key drivers of costs are the [cost of goods \(COGs\)](#) and personnel. In our review of the literature on cost of development and manufacture we found the following:

- Generally, the COGs for CAR-T are estimated at \$87,000-\$92,000 per dose.<sup>45</sup> Of that total, 57% goes to materials, 22% to labor, and 5% to other consumables. It is estimated that local manufacturing reduces cost by ~\$5,000/dose compared to centralized manufacturing.
  - Variability in those estimates is apparent when looking at the cost of goods for Yescarta, the second approved, commercial CD19 CAR-T product. The cost of production is estimated at \$58,200/dose, with a range of \$48,000-\$106,000. Material goods are estimated at 18% of COGs, labor at 71% of COGs, facilities at 8%, and equipment at 4%.<sup>46</sup>
- The CAR-T COGs in academic facilities are cheaper, with a range of \$6,000-20,000.<sup>47</sup> The difference is due to lower monitoring and QC requirements (as compared to commercial manufacturing), cheaper labor and rent, and the absence of profit margin requirements. Nevertheless, academic investigators usually cannot pay the full cost of academic facilities. And anecdotal evidence from multiple academic institutions suggests that administrators are often reluctant to provide significant ongoing institutional support.
- Using a modeling approach, Krishna and colleagues found that a cell therapy with accelerated approval for an oncology indication and three pilot (60 patients total) and two pivotal studies (300 patients total) would cost an estimated \$550M over seven

years, with personnel cost at \$245M and all non-personnel expenditures at \$305M.<sup>48</sup>

There are other cost considerations for the development of new drugs. For example, there may be a need to develop companion diagnostic tools to screen eligible patients for specific genotypes within the pool of clinically presenting patients. Small patient populations may lead to smaller trials and reduced costs but could also slow trial enrollment and increase costs.

Given the scarcity of concrete data in the literature, another approach to estimate the costs of drug development is to use the funding levels provided by the California Institute for Regenerative Medicine (CIRM) as a guidepost ([Table 3](#)). CIRM is a state agency which awards grants to advance stem cell research<sup>49-51</sup> and as we elaborate below, grants provided by CIRM are allocated based on distinct phases of development. Of note, the CIRM funding mechanisms are not enough to bring most drugs to BLA which generally requires hundreds of millions of dollars. CIRM Discovery Phase (DISC2) grants are awarded for the development of therapeutic target candidates and can be used to support laboratory and early animal studies. DISC2 grants fund direct project costs of up to \$1.5M per award and project periods may not exceed two years.<sup>52</sup> Comparable funds from the National Institutes of Health (NIH) could be in the form of R21 and R01 grants at approximately \$125,000 and \$250,000 per year, respectively. CIRM also funds Translational Phase (TRAN1) grants for awardees to take target candidates to the pre-IND stage. Over a maximum of 30 months, these grants may cover up to \$4M in direct project cost toward advancing a cell or gene therapy or other biologic. Including indirect costs, TRAN1 grants may reach up to \$6M.<sup>53</sup> The NIH also provides support for late-stage pre-clinical work and clinical trial planning for therapeutic development of small molecules, biologics, or gene therapies through the NIH UG3/UH3 clinical grant program.

Drug Development Process Through BLA				
Activity		Duration	Funding Mechanisms	Project Lead
Discovery research		2-5 years	NIH RO1 ~\$1.5M x 2-3	Academic or commercial
Proof of principle		2-3 years	CIRM DISCO ~\$1M	Academic or commercial
Define final therapeutic product		1-2 years	CIRM DISC1 ~\$1.5M	Academic or commercial
Initial regulatory interactions		----	---	Academic or commercial
<b>Getting to Phase I:</b>				
Perform pilot pharm/tox studies		1-3 years	CIRM TRAN1 ~\$4M	Academic or commercial
Establish CMC plan				
Develop clinical protocol				
Pre-IND meeting		----	----	Academic or commercial
<b>IND-enabling:</b>				
GLP Tox		1-2 years	CIRM CLIN1 ~\$6M	Academic or commercial
CMC for engineering lots				
Local regulatory reviews				
IND	Phase I	2-3 years	CIRM CLIN2 ~\$12M	Academic or Commercial
	Phase II	2-3 years	CIRM CLIN2 ~\$15M	Academic or Commercial
	Phase III	2-3 years	CIRM CLIN2 ~\$10M	Commercial
<b>Assemble BLA:</b>				
Clinical, Pharm/Tox, CMC data		1 year	~\$1-2M	Commercial
Commercial-grade manufacture				
Submit BLA		---	---	Commercial

Table 3. Drug development activity and government funding mechanisms by development phase and duration. Government funding mechanisms do not cover the full cost of product development.

To take a candidate product to IND, CIRM provides Pre-Clinical Development Phase (CLIN1) grants, which fund direct costs of up to \$6M for nonprofit entities and \$4M for for-profit organizations. Project proposals must be at a stage in development where an IND application can be filed within 24 months; applicants may also propose activities to initiate a clinical trial extending up to six months beyond the IND filing date.<sup>54</sup> Lastly, CIRM’s Clinical Trial Phase (CLIN2) grants are designed to advance drug candidates to patients. To be eligible for these awards applicants must aim to complete enrollment and dosing of all patients as well as initial analysis of primary trial endpoint(s) within 48 months. Caps for CLIN2 funding are based on the organization type and phase of clinical trial (Table 4).<sup>55</sup> Applications for similar types of grants from the NIH have to be submitted through specially designed Funding Opportunity Announcements (FOAs) designated for clinical trials.

For early phase trials, sponsors of cell and gene therapies may choose between manufacturing in an academic manufacturing facility or a CMO. The costs of these two approaches are very different, with academic operators generally charging a fraction of the commercial price. However, CMOs may provide a greater level of regulatory compliance, which can speed up later phases of development in preparation for a BLA. In addition, since many early phase trials for rare diseases are conducted at academic centers, the availability of academic manufacturing facilities is often a limiting factor.

CIRM Funding Caps			
Applicant Type	Phase 1 Feasibility Award Cap*	Phase 1/2, Award Cap*	Phase 3 Award Cap*
Nonprofit	\$12M	\$15M	\$10M
For Profit	\$8M	\$15M	\$10M

Table 4: CIRM Funding Caps<sup>35</sup> for clinical stage awards differ by phase and sponsor type.

### Unique challenges for pharmacology, toxicology, and analytical assays of CRISPR platforms

While many key steps and considerations are the same for more established classes of biologics and genetic therapies, there are challenges unique to CRISPR-based therapies that should be highlighted. The standard CRISPR technology causes double-strand breaks in genomic DNA. These double-strand breaks are generally tightly targeted to the intended genomic locus. However, in the case of off-target cuts or intentional targeting of multiple loci, there is potential for both local mutation and large scale translocations to occur. The consequences of such events will depend on the specific application. For example, the risk of oncogenic transformation from such genetic damage may be lower in T-cell based therapies, but more substantial in cell types such as CD34+ hematopoietic stem cells.<sup>56</sup>

The novelty of the mechanism of action of CRISPR-Cas in drug products means regulators must adapt their frameworks and establish new guidelines on everything from the quality of raw materials to data requirements for clinical studies. In March 2022, the FDA released a draft guidance document on gene therapy products incorporating genome editing in which the agency provides an overview of the expectations for both the materials (such as guide RNA and DNA templates) and the preclinical pharmacology and toxicology assays required for the IND application.<sup>57</sup>

For CMC, one notable requirement of this guidance document is that genome-editing nucleic acids are considered drug substances by the FDA, requiring sponsors to provide extensive characterization of the manufacturing methods, quality control testing, and activity of the materials. A September 2022 FDA/OTAT Town Hall Session<sup>58</sup> corroborated the expectation that viral vectors and gene editing reagents cannot be “Research Use Only” designated materials, but must have more complete quality information to be considered appropriate, even for trials in rare diseases where the total market size is small and patient tissues are difficult to obtain. This expectation increases barriers to development of CRISPR-based therapies for rare indications, since the prices of high-quality materials produced by CMOs may be out of reach for the academic groups that generally pioneer therapies for rare diseases, and it may not be cost effective to develop product specific reagents onsite. In addition, contract suppliers are often unmotivated or unwilling to support small-scale projects.

For pharmacology and toxicology studies, the FDA expects detailed analysis of off-target cut sites, including potential translocations. This requirement involves in-silico, in-vitro, and next generation sequencing-based analyses including assessment for potential oncogenic modifications. Very few academic groups in the world have the required expertise to perform this work, and even fewer groups - academic or commercial - have the experience of generating

this data at the [Good Laboratory Practice \(GLP\)](#) quality required for eventual BLA. For CRISPR-based knock-in, we are aware that the FDA has also requested characterization of on- and off-target knock-in events and to analyze specific sequences of successful knock-ins. We expect that next-generation CRISPR-based editors (e.g., base editors and prime editors) will require similar regulatory documentation.

An additional barrier to generating high-quality preclinical pharmacology and toxicology data is the need to use model systems such as cell lines, small animal models, and cells from “healthy donors” rather than patients with the relevant disease. Although the FDA does encourage using the most relevant model, some widely-used models such as NSG mice (used for many human cancer models) have limited relevance to human biology. Crucially, model system genomes vary from the human reference genome, requiring the creation of a proxy therapeutic that targets a mouse or primate analog in order to generate necessary safety data. Rare genetic diseases face a similar challenge since tissues and cells with the relevant mutations are difficult or impossible to obtain in quantities large enough for preclinical studies.

Delivery of genome editing materials to cells and tissues can be done [ex vivo, in vivo, in situ](#), and with or without viral vectors. These variations add additional complexity to the regulatory and quality expectations for products in development. The FDA expressed its regulatory stance on these very different approaches in a 2020 FDA guidance document.<sup>59</sup>

### International approaches to lower-cost cell and gene therapy manufacturing

Governments of countries in which most residents are covered by a publicly funded healthcare system face challenging decisions on whether to cover the steep price of cell and gene therapies or to keep patients on the current standard of care which is often limited to symptom management. Even in high-income countries, finite healthcare budgets mean the value of a targeted, high-cost therapy has to be weighed against standard of care costs; any additional expenditures have to be evaluated against the implications for healthcare access for all beneficiaries of the system. As discussed in [3. Pricing and Access](#), government entities like the National Institute for Health and Care Excellence in the United Kingdom make such decisions on a case-by-case basis. Governments have also been able to negotiate discounted prices, although disagreement on price with the manufacturer may ultimately mean a life-saving therapy cannot be accessed. In Brazil, where a right to health is constitutionally enshrined, over 100 lawsuits from patient families have forced the government to cover Zolgensma, a gene therapy for spinal muscular atrophy, at a price of about \$1M per patient.<sup>60</sup> Around the world, the numerous genetic therapies that are already surpassing Zolgensma in list price will undoubtedly stretch public funds for healthcare, if they are made available at all. [Box 1](#) and [Box 2](#) highlight two approaches taken by countries outside of the USA to address the affordability and access problem.

### **Box 1. Made-in-Canada CAR-T Cells, a government-backed initiative led by the immunotherapy network BioCanRx**

In Canada, currently, licensed cellular therapy products (i.e., Health Canada-approved drugs such as Kymriah or Yescarta) are paid for through provincial health care budgets at a significant cost to taxpayers. Each provincial government determines the availability of such treatments and the onboarding of new treatments based on clinical and administrative recommendations. Once a treatment is approved for standard of care use, access is provided based on clinical parameters.

BioCanRx, a network of centers of excellence funded by the federal government with support from provincial governments, charities, and industry partners, is focused on translating research into early phase clinical trials. BioCanRx and its partners have invested in point-of-care (POC) manufacturing infrastructure, the development of novel viral vectors and CAR-T immunotherapies, and clinical trials.<sup>61</sup> POC manufacturing capacity has been established in British Columbia, Ontario, Manitoba, Saskatchewan, New Brunswick, and Alberta. So far, the federal government has spent over \$10M and partner contributions have totaled over \$16.5M.<sup>62</sup>

All cell and gene therapies must be approved through Health Canada and there is ongoing work to determine a more efficient route for approval of POC manufactured products. Licensing and approval of these cell and gene therapies is of utmost interest to the provincial and federal governments as it would significantly improve affordability of these treatments and reduce costs to taxpayers. The manufacture of an autologous CAR-T therapy in the POC model in Canada is estimated to cost between \$35,000 and \$50,000. In comparison, Novartis' Kymriah, an approved, commercially available CAR-T product, is priced at \$475,000 in Canada.<sup>63</sup>

BioCanRx has in place two major clinical trials employing point-of-care manufacturing platforms for CAR-T products for infusion. This "Made-in-Canada CAR-T" platform program uses a GMP-enabled manufacturing device to produce a cell therapy dose in 7 to 10 days, and has already been used for more than 50 patients at less than a tenth of the cost of a commercial product. In Alberta, the provincial government contributed \$10M of the total \$15M investment to create the Made-in-Alberta platform; the Alberta Cancer Foundation contributed \$5M to initiate the clinical trial. It is anticipated that the \$15M investment will be recovered within six months of rollout of an approved product in the province of Alberta. The Canadian government has also contributed significant funding to infrastructure and clinical trial support to promote cell and gene therapy manufacturing in Canada at POC.

Beyond CAR-T cells, POC equipment can also be modified to deliver genome editing reagents to cells, which may ultimately pave the way for publicly funded hospitals and research centers to manufacture more therapies. Along with the outsized benefits of curative treatments to patients and society, investments in research, know-how, and infrastructure today may prove a long-term, cost-saving strategy for publicly funded systems.



## Box 2. Brazilian-centered perspective on cell and gene therapy affordability

The aspiration of delivering effective, advanced cell (not including hematopoietic stem cell transplantation) and gene therapy for patients in LMICs is tempered by concerns of cost. CAR-T therapies to treat relapsed and refractory hematological malignancies (B-cell acute lymphoblastic leukemia, B-cell non-Hodgkin lymphomas, and multiple myeloma), appear cost-effective in most analyses performed in high-income countries. However, given the current price tags, it is certain that LMIC governments will be unable to finance advanced cell and gene therapies within their public health systems.

In Brazil, despite the approval of three commercial CAR-T cell products by the health authority agency (ANVISA), payers, insurers and hospitals are facing financial and logistical hurdles. To address the challenges the Brazilian public health system, the government of the State of São Paulo (a high-income region in Brazil), in collaboration with the University of São Paulo, the Butantan Institute, and São Paulo Foundation of Research (FAPESP), has invested approximately \$30M to produce an academic CAR-T cell therapy at two sites. Both manufacturing facilities have been built and CAR-T cell products are being manufactured. This initiative will allow patients with hematological malignancies covered by the public health system to be treated. Ten patients with relapsed and refractory B-cell malignancies have already been treated under compassionate use with great success. The same strategy is being considered for future application of gene therapy to treat patients with sickle cell disease, a prevalent disease in Brazil. However, the high costs of viral vectors remain a significant barrier to development.

### Approaches to shorten timeline, reduce costs, and increase access

**Platform manufacturing approaches.** The development of standardized platforms for cell and gene therapy manufacturing is a critical element of bringing down costs. Although many research protocols for CRISPR-mediated human gene editing have been published, the corresponding GMP-compliant protocols are generally not published and considered trade secrets by academic groups and biotechnology and pharmaceutical companies. Therefore, each group developing a new product must reinvent basic elements of their manufacturing process. One potential solution to this is the development of platforms that can be used for common processing steps such as target cell selection

(e.g., using CD34 or CD4 markers), cell culture, and cell harvesting steps. Platforms should ideally be based on widely available technology where multiple vendors can supply the critical reagents. Such an open-source approach has been very successful in the world of software engineering where commonly used components of programs have been refined and widely shared for general use. Standardized platforms will also facilitate review of large portions of the CMC by regulators, and thus reduce review times, since they will be familiar and already proven in other trials. However, commercial considerations may stymie widespread adoption of platform technologies since intellectual property protection of one piece of a process may prevent broad adoption.

To help advance platformization and reduce the burden of process development and associated regulatory approval steps, the NIH's National Center for Advancing Translational Sciences (NCATS) has launched the Platform Vector Gene Therapy (PaVe-GT) pilot project. During this project, a standardized process with the same AAV capsid and manufacturing method will be employed to treat four different rare diseases. Investigators will make data on IND filings, biodistribution data, toxicology, and communications with the FDA publicly available.<sup>64</sup> A public-private partnership managed by the Foundation for the NIH, known as the Bespoke Gene Therapy Consortium (BGTC), is similarly conducting studies to develop standardized analytic tests for viral vector manufacturing and investigate how regulatory processes could be streamlined, for example by establishing standardized preclinical tests.<sup>65</sup> Further upstream, and more focused on genetic therapies, the Somatic Cell Genome Editing Consortium comprises dozens of investigators working to improve the tools and techniques for safe and effective genome editing and delivery, and enhance cell-type and tissue specificity.<sup>66</sup>

### **Distributed versus centralized manufacturing.**

Currently, the accepted model of cell and gene therapy manufacturing follows the traditional pharmaceutical industry model of large, centralized plants in a few locations globally. For autologous therapies in particular, this model creates enormous logistical hurdles and prolongs manufacturing times, which limits access ([Box 2](#)).<sup>67</sup> Therefore, distributed manufacturing of cell and gene therapies could overcome these limitations.

In centralized manufacturing, a patient's blood cells are collected in a hospital and typically cryopreserved for shipment to a centralized facility (although logistics can allow for shipment of non-cryopreserved products) where the drug product is manufactured in clean rooms, cryopreserved again, shipped back to the hospital, and thawed bedside immediately prior to patient delivery. The centralized process has the advantage of reducing assay-to-assay variability because product quality and release can be rigorously assessed onsite at testing facilities. However, the logistical burdens associated with shipping and storage throughout this process invariably drive up the cost.

In the point-of-care model, the cell product is manufactured within the hospital or associated facility, such as an academic GMP facility. Like the centralized process, this process begins with blood collection from the patient, but then uses an automated, closed-system device to isolate cells, genome-modify them, expand the modified cells to sufficient numbers needed for a dose, formulate the final cell product, and deliver to patient via infusion. In contrast to centralized manufacturing, point-of-care manufacturing imposes minimal logistical burdens given that the process is limited to the number of patients in the hospital. It also leverages cell manufacturing expertise intrinsic to academic medical centers. Another major advantage is the absence of the cryopreservation steps for both the collected cells and the final infusion product, allowing a rapid turnaround of an immediately active product for patients with advanced disease.<sup>68,69</sup> Thus, POC manufacturing precludes the need for multiple layers of oversight to ensure proper shipping and storage, which significantly reduces cost.

The widespread adoption of standard of care hematopoietic stem cell transplantation across the world is an example of distributed manufacturing. Although some companies such as Miltenyi are pursuing distributed manufacturing models for gene therapies, the regulatory barriers remain formidable. In particular, showing that processes and products at different manufacturing sites across the world are comparable is very challenging and may be impossible. Given these hurdles, the FDA published a discussion paper<sup>70</sup> on distributed and point-of-care manufacturing of drugs and biologics with a request for public information and comment in October 2022. Distributed manufacturing is a worthy goal but has major challenges such as the ability of staff to demonstrate process comparability, appropriate quality oversight, recruitment and retention of trained staff, and the ability to test and release a product.

### **Closed and automated manufacturing systems.**

Finally, labor costs are a major contributor to manufacturing costs and shortages of trained personnel hinder scale-up of manual manufacturing processes. Closed, automated manufacturing using robotic systems has the potential to decrease labor costs and increase capacity without the need to build expensive cleanroom laboratories. Although there are many instruments on the market that automate parts of the manufacturing process, the promise of fully robotic manufacturing and quality control testing for cell and gene therapies is still distant.

**Non-viral methods for gene modification.** Non-viral gene editing methods may have superior clinical efficacy due to targeted genomic integration.<sup>71</sup> This approach would avoid some of the major drawbacks of viral vector-based CAR-T manufacturing approaches. Production of viral vectors is expensive, has long lead

times at existing manufacturing facilities, and may add years-long delays if problems with a specific batch of vectors are identified. In contrast, non-viral approaches use nucleic acids and proteins as the critical materials, which are easier to manufacture at GMP quality. Therefore, alternative non-viral approaches to genetic modification using CRISPR technology are appealing options to increase the pace of innovation while decreasing cost of development and delivery.

One approach to non-viral genome editing with CRISPR uses a partially double-stranded DNA template to knock a CAR sequence into the T cell receptor alpha locus.<sup>72</sup> This approach could easily be extended to knock in many different genes at this locus with the only variable being the DNA template sequence. Despite the promises of non-viral methods, there are unique barriers to this approach as well. For example, despite the target of this particular CAR being well-established with a commercial CAR on the market, the FDA has still requested a full panel of pharmacology and toxicology studies due to the novelty of the manufacturing platform, increasing the costs and development time. In addition, the partially double-stranded DNA template is not widely available at GMP quality is very costly, posing barriers to academic groups looking to use the technology.

In summary, although CRISPR technologies have tremendous potential to decrease costs and increase access to genetic therapies, significant manufacturing and regulatory challenges remain to advance products to Phase I trials.

### Conclusion

Manufacturing challenges and regulatory requirements are significant drivers of cost. Both in academic and commercial settings, manufacturing capacity is limited and the pace of new cell and gene therapy will be slowed unless funding is directly allocated to expand the skilled workforce and build adequate infrastructure. Critically, CIRM is leading in this arena as evidenced by its recent \$80M to create a public-private, California-wide network of academic process development and GMP manufacturing facilities.<sup>73</sup> Regulatory requirements on analytic, pharmacologic, and toxicologic assays are critical to ensuring safety, yet costly and complex for cell and gene therapies. Standardized platform

technologies could mitigate these challenges and should be open-source so academic and industry players can adopt them without supply chain concerns or IP barriers. As shown in the Canadian model ([Box 1](#)), point-of-care manufacturing also has the potential to drastically reduce manufacturing cost and increase access. These approaches, coupled with closed and automated manufacturing processes could shorten the time to develop new products and enhance scalability. Improvements in and adoption of CRISPR-based solutions with shorter manufacturing lead times and lower costs of goods will also prove essential to the mission of greater affordability and access.

# 5. INTELLECTUAL PROPERTY (IP) AND LICENSING

[Academic institutions](#), including research universities, non-profit research institutions, and government research laboratories as originators of novel therapeutics, diagnostics, and other health technologies file patents to protect ownership of their intellectual property (IP). In our current system of developing and commercializing healthcare technology, intellectual property provides the necessary temporary exclusivity to promote investment in translating the discovery to a marketed product. The Bayh-Dole Act sought to eliminate uncertainty of IP ownership by statutorily conferring ownership in inventions made with government financial support to the grantee institution, while reserving certain rights for the US government. Academic institutions can thus exert leverage on the patent's use through the terms of licensing agreement and know-how, ultimately impacting access for [patients](#) worldwide. The challenge is that those institutions and the [technology transfer offices \(TTOs\)](#) representing them in negotiations with commercial companies are often incentivized to consider only the number of patents filed, licensing agreements signed, and royalties received as metrics of their success. The availability of the medical interventions to patients in need, including in low and middle-income countries, may not be considered as a metric of success by such calculations. Motivating TTOs and more importantly, university administrations to value those achievements is a first step in increasing access to products.

## Scope

The goal of this subgroup is to describe the role that intellectual property licensing could play in promoting access (affordability, availability and sustainability) to [genetic therapies](#) and

potentially other life-saving therapeutics around the world, and to delineate recommendations to academic [technology transfer offices \(TTOs\)](#) that will mitigate the enormous challenges to access to life-saving or life-changing therapies. We examine this question of promoting access in [low- and middle-income countries \(LMICs\)](#) as well as in high-income country markets with large populations lacking access to many therapies, including those within the United States.

## Recommendations

In order to improve affordability and access to medical therapies generally, irrespective of a particular market, we advocate that academic institutions focus on adopting practices related to:

- The creation of additional license provisions relating to items including: company generated access plans, audits, and other licensee obligations, extending after first commercialization (standard practice), with implementation of routine milestones along the drug development and commercialization process to inspect completion of these obligations. These could be pilot tested in negotiations with potential licensees where the end product is clear, and then added to earlier stages of licensing agreements.
- Tracking the success of these obligations and other related provisions to increase data and metrics on their use and impact in order to evaluate, report and refine these additional provisions.
- Lobbying for university executive-level (trustee-level) support for TTOs to add affordability and access provisions in their licenses, increase personnel and financial support for these activities, including tracking, and advocate to promote a common framework for access across

academic institutions. Supporting increased transparency by publishing copies of licensing agreements that are redacted solely to the extent required to protect the commercially sensitive information of the licensee. This will promote and reinforce norms for the inclusion of access-related terms in institutional licensing agreements going forward.

### For LMICs

We recommend enacting institutional policies that require licensees to develop access plans as part of all licensing agreements that will facilitate the distribution of affordable licensed medical products in LMICs. These plans, depending on the licensee, may include mechanisms such as:

- A limitation on geographic exclusivity so that licenses are non-exclusive in LMICs, unless the licensee is willing to commit supplying products in LMICs themselves on an affordable basis;
- A requirement that sublicenses or license grants be made to specific organizations such as the Medicines Patent Pool or public development partnerships to develop and make licensed products available to all countries in need (licensing intellectual property when needed);
- A requirement to develop licensed, affordable products that are registered in all needed markets, and supplied in a timely manner to LMICs;
- A policy not to file or enforce patents in low-income countries; and
- Enforcement mechanisms for the above.

### For US markets

In the United States, enhanced affordability and access could be achieved by incorporating mechanisms such as the following in access plans:

- Increased efforts by TTOs to negotiate and enact a “most-favored nation” clause<sup>74</sup>, such

that US patients would not be charged more than other high-income country markets;

- Adoption of licensing provisions by academic institutions which support access for particular populations in the US (e.g., Medicare and Medicaid beneficiaries, uninsured patients, veterans);
- The institution of license agreement provisions that require price reductions once certain volumes are sold, or substantially increase royalties in the absence of volume-based price reductions (similar to provisions in the Inflation Reduction Act of 2022 that require rebates from companies when they increase drug prices above the rate of inflation);<sup>36,75</sup>
- Conversion of exclusive licenses to non-exclusive licenses if FDA post-approval studies or further research and development (R&D) on new indications are not completed within negotiated time periods

### Background: Academic technology transfer offices

Technology transfer offices (TTOs) and related university offices are usually the gatekeepers to the basic intellectual property that underlies medical innovations. TTOs are uniquely positioned to leverage their position to facilitate access for patients globally who could benefit from their patented technologies. IP licenses negotiated by TTOs typically include terms that directly impact how and where successful technologies are developed and made available, as well as the costs of a patented product in different markets.

Another aspect that is controlled by academic TTOs is the choice of licensee. Usually, an (academic) inventor defines the potential market(s) for their invention to generate interest in filing a patent from their institution’s TTO. The TTO subsequently evaluates potential licensees upon disclosure of the invention. Most TTOs do not have sufficient technical knowledge in all

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areas to assess potential markets, much less to determine if potential products would have both financial and medical value outside of high-income markets. Although one of the greatest challenges to TTOs is finding a licensee for more obscure technologies, valuable innovations pose considerable challenges too.

Many academic institutions and their TTOs are reluctant to include access provisions and obligations into negotiated agreements despite many years of discussions (Box 3). Students and researchers, especially through Universities Allied for Essential Medicines (UAEM), have pushed TTOs to support efforts to increase access to the medical products resulting from their innovations.

In 2007, 11 major US research academic institutions and the Association of American Medical Colleges signed an accord<sup>76</sup> titled “In the Public Interest: Nine Points to Consider in Licensing University Technology.” The accord highlights issues that should be considered by academic institutions when negotiating licensing agreements with private entities. The Nine

Points document dealt with a range of issues such as reservations of rights and limitations on exclusivity, limiting dealings with patent assertion entities, and making medical technologies accessible at affordable prices. Importantly, the accord proposed specific contractual clauses that would advance the educational and public welfare missions of academic institutions. Over 100 academic institutions and associations around the world have signed the document.<sup>77</sup>

Recently, researchers empirically evaluated the impact of the Nine Points document by reviewing 220 publicly available university technology licenses. Findings suggested that “while the document prompted the expansion of educational and non-profit research using patented university technology, it resulted in few changes relating to the promotion of public health or access to medical technologies.”<sup>77</sup> Mixed adoption of the Nine Points recommendations signaled that there is little consensus regarding the nature of ‘public interest’ and highlighted the necessity of “reorienting university technology transfer policy”.<sup>77</sup>

### Box 3. Therapeutics for spinal muscular atrophy

Spinal muscular atrophy (SMA) is a hereditary genetic disease that results in progressive deterioration of certain muscular functions, leading to severe disability or death. An estimated 2% of the population are considered carriers. Estimates of the incidence of SMA vary from 1 in 6,000 to 1 in 12,000 live births. Beginning in 2016, the US [Food and Drug Administration \(FDA\)](#) has now approved three important treatments for SMA, including two drugs, nusinersen (trade name Spinraza) and risdiplam (trade name Evrysdi), and one gene therapy, onasemnogene abeparvovec (trade name Zolgensma).

Spinraza was developed at the University of Massachusetts and Cold Spring Harbor, funded by NIH grants, and licensed to Biogen, which marketed the drug at a price of \$750,000 in the first year and \$375,000 per year for maintenance doses. The second product, risdiplam, was developed by the US-based Spinal Muscular Atrophy Foundation through research contracts with PTC Therapeutics and later Roche. Roche now markets the drug globally under the trade name Evrysdi at an annual price of \$340,000. Sales of Evrysdi in 2022 were \$1.119 B dollars, an increase of 86% over the previous year.<sup>78</sup>

The gene therapy Zolgensma is a one-time treatment for patients less than two years of age. Zolgensma was first developed at Nationwide Children's Hospital (NCH), relying on a combination of several SMA charities and the NIH to fund the research. After Zolgensma showed promise, the technology and the NCH patents were transferred to a company called AveXis, which had been repurposed to commercialize the gene therapy. AveXis licensed three additional gene therapy patent portfolios, including one involving NIH-funded inventions at the University of North Carolina (UNC) and one from NIH-funded inventions at the University of Pennsylvania (UPenn). Both the UNC and UPenn patent families had been spun off by their institutions into for-profit companies, which then licensed to AveXis. The fourth patent license was from Généthon, a nonprofit research organization supported by the French Muscular Dystrophy Association (AFM-Téléthon). In 2018, AveXis was acquired by Novartis for \$8.7B. Novartis placed Zolgensma on the market for a price of \$2.1M. Among the various [funders](#), only one, AFM-Téléthon, placed conditions on the pricing of the new gene therapy concerning French patient access. This obligation is included in Section 4.5 of the Généthon/AveXis license<sup>79</sup>, demonstrating the power of appropriate licensing provisions for the public good, and showing that pharmaceutical companies are willing to accept such language:

4.5. French Patient Access. Following the appropriate regulatory approvals, Licensee will use Reasonable Efforts to make available within France all the Licensed Products indicated for SMA at prices that would allow appropriate reimbursement schemes and that would not constitute an obstacle for patients to have access to the therapy. Licensee shall be solely responsible for designing and conducting all Commercialization activities necessary to fulfill its obligations under this Section 4.5.<sup>79</sup>

These products are very expensive, such that availability is often constrained by insurance coverage and patient access globally is generally localized to the major markets. Compassionate access



programs do exist in some countries but are limited in scope. In July 2022, Knowledge Ecology International asked Roche to provide a voluntary license to the risdiplam patents to allow the production and distribution of an affordable generic version for patients in developing countries where the drug is generally not accessible due to its high price.<sup>80</sup> In August 2022, Roche rejected the license request.

Each of the three SMA treatments received an FDA [Priority Review Voucher \(PRV\)](#) for Rare Pediatric Disease Products upon initial registration. The FDA PRVs are transferable, and in recent years, have sold for between \$80 and \$130M. Each of the products also benefited from the US federal government [Orphan Drug Tax Credit](#). There are no conditions on the PRV or the Orphan Drug Tax Credit regarding pricing or access.

### Patent licensing procedures

In the 1980s, Congress passed a law that came to be known as the Bayh-Dole Act (Pub.L. 95-517). Prior to its implementation, the US government had ownership of patented inventions that arose from federal funding. In 1978, the Government Accountability Office (GAO) estimated that the US federal government owned over 28,000 patents, but had only licensed about 5% of them. The Bayh-Dole Act gave academic institutions and other federal grant recipients the right to claim ownership and more freely manage patents from inventions that arose from federal grant funding. The original Act limited the period of exclusivity to five years from first commercial sale or use of the invention or eight years from the date of the exclusive license. However, in 1984, Congress amended the Act (Pub.L. 98-620) to give academic institutions and other grantees the right to use exclusive licenses for the life of patents.

Also included in this Act was the concept of ‘march-in’ rights retained by the federal government (35 U.S.C. § 203). March-in rights give the funding agency the right to “grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants” (35 U.S.C. § 203), but only if the patent holder is found to have failed in one of four areas:

1. The patent holder had not “achieved practical application of the subject invention.” Practical application requires that the benefits of the invention are “available to the public on reasonable terms.”
2. The federal agency felt that this action is necessary to address health or safety needs.
3. The federal agency felt that this action is necessary to meet requirements for public use specified by Federal regulations.”
4. The patent holder fails to manufacture a product “substantially in the United States.”

Since the time this Act was put in place, the federal government has not formally invoked these march-in rights, despite several petitions requesting the government to act.<sup>81</sup> In a handful of cases, the patent holder has made concessions to avoid the march-in remedy from being used. Some examples include the Cellpro<sup>82</sup> and Fabrazyme<sup>83</sup> cases in which injunctions on infringing products were withheld to protect the supply to the public. The US Centers for Disease Control and Prevention (CDC) has explored the use of Bayh-Dole rights to ensure that patented inventions were licensed to manufacturers of vaccines for Avian flu. Additionally, the National Institutes of Health (NIH) reportedly used the threat of march-in rights to pressure the University of Wisconsin Alumni Research

Foundation (WARF) to provide more liberal access to stem cell patents, following President Bush's decision in 2001 to restrict federal funding of research on new stem cells.<sup>84</sup>

There continues to be debate around the intent of the Bayh-Dole Act with some calling for Congress to clarify the government's march-in rights authority, while others have urged federal agencies to harness march-in rights as an appropriate tool for enabling access. The basic science of several of the most transformative medicines, vaccines, and diagnostics have been discovered at academic institutions through the use of federal funding. Indeed, a recent study suggests that total investments by NIH in drug development, in the form of basic and preclinical research funds, are similar to those of the pharmaceutical industry.<sup>85</sup> A key question is how the basic patents on these technologies – originally discovered through taxpayer funding – should be managed with respect to pricing and access in the US and around the world.<sup>86</sup> Some have argued that the Bayh-Dole Act is an example of the government's unwillingness to protect the public's interest in public-private partnerships.<sup>87</sup> Meanwhile, attempts from within Congress to urge the use of march-in rights to lower drug prices have received strong and consistent opposition from a lobbying coalition<sup>88</sup> of academic institutions, drug companies, and venture capital firms. In March 2023, coinciding with another rejection by NIH of a request to use march-in rights to lower the price of Xtandi<sup>89</sup>, the Department of Health and Human Services and the Department of Commerce announced an interagency working group that they will review implementation of march-in rights and develop a framework with clear guiding criteria and processes for agencies when making determinations about exercising march-in authority.<sup>90</sup>

Given that the Bayh-Dole Act allows academic institutions to control the licensing of their intellectual property, and modifications to the Bayh-Dole Act could impact institutional income from licenses, there is an inherent conflict between the goals of equitable public access and an institution's goals to generate the highest amount of licensing income from its IP, particularly as public funding for Universities has decreased over time. Ideally, academic institutions should implement licensing provisions that would ensure that licensees meet reasonable obligations for access.

### **Barriers for implementation of access provisions in university licenses**

Institutional unwillingness to change the status quo presents additional challenges to implementing access provisions in licenses. TTOs may fear potential pushback from industry licensees against such efforts and may be concerned that this could have a chilling effect on their ability to solicit future licensees. The proper execution and implementation of access provisions also require substantial resource investments, including human and financial capital as well as technical expertise. In addition, the impression that the nature of a technology, its stage, or the type of collaboration can preclude access commitments acts as a disincentive to attempting such negotiations. A lack of data and metrics around positive public opinion and real-world outcomes as a result of such provisions further act as a barrier at all levels.

Nonetheless, there are indications that shifts in mindset and implementation are starting to be accepted. Broader knowledge of the use of, as well as tools to ensure access through licensing are contributing to this shift. For example, the TTO personnel at the University of California, Berkeley have published articles delineating ways to improve university licensing practices for access.<sup>91,92</sup>

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There is greater support for access policies as well as an increased willingness by TTOs to discuss possible first step options that may improve affordability to future patients. There has also been a movement to incorporate due diligence obligations beyond initial product commercialization. These obligations could include audits, enforcement, and the conversion of exclusive licenses to non-exclusive licenses where markets are not adequately addressed. An example of this has recently been implemented at the University of California, Berkeley, and by the University of California, Los Angeles using Affordable Access Plans that require licensees to submit plans for enabling access across LMICs.<sup>93</sup> UC Berkeley's Affordable Access Plan also includes provisions relating to licensees providing access to vulnerable, underserved and special needs populations in the United States.

Thus, given this shift among university TTOs to prioritize access, we focus on specific recommendations for licensing provisions that can be designed to enable and increase access and affordability in both LMICs and the United States. These provisions, used early in the licensing process and also allow universities through drug development and commercialization pipeline to ensure their implementation, can precipitate lasting changes that would make academic medical technologies affordable and widely available to the markets in need.

### **Improving transparency and providing access in LMICs**

Access to genetic therapies in LMICs has been improving, but the numbers of patients treated are negligible to non-existent.<sup>94,95</sup> This is due to a range of economic and logistical obstacles. For example, local facilities have limited or no capacity to manufacture and distribute biologics or reagents for genetic therapies. Agreement

provisions supporting increased affordability and access in LMICs are often absent and, if present, ineffective. Additionally, they are neither tracked nor enforced.

Enabling policies could include those that limit geographic exclusivity such that licenses are non-exclusive in LMICs if the primary licensee is not equipped or prepared to commit to seeking marketing authorization and distribution in those markets. TTOs could also grant licenses directly (or require that licensees grant sublicenses) to parties such as the Medicines Patent Pool, a United Nations-backed non-governmental organization created to increase access to affordable medicines in LMICs primarily through the use of patent pooling and voluntary licensing, for the purpose of making licensed products accessible and affordable to those countries in need.

Granting a license for an early-stage technology to a third party may require anticipating certain challenges. The licensed technology may not be, and likely is not, sufficient on its own to enable development and manufacturing of an approvable product. The development work that the licensee performs will generate know-how, regulatory data, potentially patentable discoveries, and potential trade secrets valuable to or necessary for the final product profile and manufacturing process. Thus, TTOs should require that affordable access plans include all intellectual property generated during the development phase such that a third-party has all that is needed to manufacture and distribute the products, or, as with the Medicines Patent Pool, to sublicense to manufacturers to facilitate such activities. For instance, in the template language adopted recently as part of [University of California Los Angeles](#) and [University of California, Berkeley](#) licensing agreements, licensees are required to develop affordable access plans for a licensed product rather than an individual licensed patent.

Moreover, as part of a licensing agreement, institutions could develop exemplary plans to guide licensees in the development of these plans, and should require an affordable access plan that commits the licensee to develop products that are affordable, registered in all needed markets, and supplied in a timely manner to LMICs. Licensees should be required to provide an evolving plan during the development process (e.g., upon reaching milestones in product development such as clinical trial phases) and agreements should include a reversion of rights in the event that the institution and the licensee are unable to reach agreement on a satisfactory access plan with performance standards.

The access plan should also outline how an end product will reach countries and patient populations in need, along with associated timelines. As a first step toward enabling access, licensees should be required to file for regulatory approval in LMICs and enter into bilateral, non-exclusive sublicenses to manufacture and provide products at affordable prices in those countries. Technology transfer should occur if the licensee does not make the product available for sale within a certain time (e.g., 18 months) following market authorization from an initial/relevant regulatory authority. Such timelines should be specified in any access plan.

The onus on a TTO to ensure compliance with access terms may exceed the office's capacity. Evaluating proposed affordable access plans may require specific public health knowledge that a TTO does not have, and tracking launch activities globally, often in jurisdictions without institutional patent protection, may be an unattainable layer of responsibility for the TTO. One approach to mitigating these concerns is for university licenses to leave room for the TTO

to lean on the public health expertise of third parties. For example, an entity with expertise and experience in such evaluation could be brought in to assist a TTO with ascertaining suitability of a proposed affordable access plan for LMICs as well as in subsequent inspections on the licensee's progress toward achieving agreed upon access goals.

Licensing agreements should be published by academic institutions, with as few redactions as possible to protect commercially sensitive information, in order to reinforce norms that nonprofit institutional licensing agreements should contain access-oriented terms and be made available to the public.<sup>F4</sup> This may also avoid challenges from institutional leadership based on an incorrect understanding of licensing standards or an inordinate focus on near-term institutional income. Ideally redaction would be restricted to truly commercially sensitive information of the licensee, such as atypical development plans, proprietary (to the licensee) formulation technology, commercial priorities, or any other information that differs from standard processes. Financial terms should remain unredacted because requests for access provisions are likely to impact financial benefits, such that disclosing one without the other would fail to provide a workable example of how access terms can be successfully incorporated into a licensing agreement.

### **Access and accountability in the US market**

Barriers to affordable access to novel treatments are not specific to LMICs, but are also increasingly apparent in the immediate vicinity of the university campuses where these health technologies are discovered and developed. Through licensing agreements academic

<sup>F4</sup> This has indeed been the case with the Medicines Patent Pool with whom both universities and industry have signed license agreements that are published without redaction.

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institutions could take more meaningful and complementary steps toward improving domestic access. This might include specific provisions focused on the downstream price of the genetic therapy. For instance, a “most-favored nation” clause could be included in a licensing agreement such that US payers cannot be charged more than those in other high-income country markets. Such a clause has been included in procurement contracts between the US government and Pfizer for Paxlovid, prohibiting the manufacturer from charging the US a higher price compared to a handful of other countries.<sup>96</sup>

It may be the case that investors of potential licensees are hesitant about such access provisions. However, the commercialization opportunity of the product and the associated intellectual property could give the university sufficient leverage to include such provisions, particularly if the product is not licensed too early in the development process, but rather when a potential indication is clearer. For genetic therapies especially, academic institutions likely have a robust understanding of potential applications given their role in late-stage development.<sup>97</sup>

In addition, academic institutions should adopt licensing language that would enable improved and more access to certain populations in the US including Medicare, Medicaid, and Veterans Health Administration beneficiaries as well as those who are under- or uninsured. One mechanism to enhance access for these populations could be for academic institutions to require manufacturers to establish payer-established and maintained patient assistance programs that are meaningful, easy-to-navigate, and with minimal eligibility barriers. However, these programs would not be solely sufficient to enable affordable procurement prices for payers and likely would only mitigate downstream cost-sharing concerns for patients.

Through licensing agreements, TTOs could employ other mechanisms to further promote affordability to university-developed medical products. This may include:

- Conditions on royalties for implementation and evaluation of access provisions and licensee efforts to provide affordable access; this should be tied to reporting and accountability structures such that licensees would be required to provide the university with routine updates that specifically address the development and implementation of their access provisions.
- Time-associated benchmarks where for instance, institutions could include provisions that
  - require price reductions once certain volumes of a licensed product are sold, possibly including a reduction in royalty rate to offset part of the profit lost from the discount;
  - tie prices to the completion of robust studies confirming clinical benefit, thus enabling more affordable access to genetic therapies where there may be continued uncertainty of clinical benefit and long-term safety, but also incentivize manufacturers to complete these confirmatory studies in a timely manner;
  - convert exclusive licenses to a single [sponsor](#) to non-exclusive licenses when the licensee fails to complete such post-approval studies within a pre-negotiated period of time or should the licensee fail to engage in further R&D on new indications.

### Conclusion

University TTOs can and should be critical leverage points upstream in the drug development process to enable access to expensive novel health technologies both domestically and globally. As discussed, although university TTOs often profess to support accessibility provisions in their intellectual property licensing agreements for groundbreaking research and drug candidates, many face challenges in enacting and/or enforcing basic licensing provisions that would ensure such access. TTOs often lack

the necessary resources to translate adopted principles around enabling access to university-developed technologies into actionable and implementable licensing provisions as well as to enforce due diligence obligations. Thus, we challenge university executives to empower their TTOs to include and implement robust licensing provisions that would better enable access to treatments for all those who need them, rather than just those that have the financial means to do so.

## 6. ORGANIZATION AND FUNDING MODELS

In this section, we set out to explore options for business and [funding](#) models that can deliver [genetic therapies](#) at a cost to [patients](#) and the healthcare economy that is sustainable across the myriad potential applications of gene-editing therapies. We evaluate innovative organization and funding models that would allow [academic institutions](#) or mission-oriented organizations to advance affordable and accessible genetic therapies. Originally, discussions centered around whether therapies for rare disorders could be developed and distributed solely via academic partnerships. While this remains a potential approach for ultra-rare disorders, or drugs undergoing early-stage clinical trials, as discussed in [4. Manufacturing and Regulation](#), academic institutions are not well equipped to hold [Biologics License Applications \(BLAs\)](#) and to manufacture to [Food and Drug Administration \(FDA\)](#) standards for widespread distribution. Instead, a strategy that takes advantage of the unique skill sets of independent business entities, while better aligning incentives, would be better suited for this purpose.

Given the challenges of raising sufficient capital and generating self-sustaining revenue, we propose a mixed organizational model consisting of several organization types that can access different types of funding at various stages of the process. With a governance framework that guarantees the pursuit of the common public benefit, combining different models can leverage the benefits of each organizational type. Some organizations have successfully employed a hybrid business model aligned with variable financing sources, providing a framework for others in the space ([Box 7](#)).

### Scope

As it stands, funding of basic research and preclinical studies by NIH, NSF, and others works relatively well to drive discoveries and biotechnological innovation, with the NIH budget steadily increasing.<sup>98</sup> However, even if academic institutions or smaller biotechnology companies are able to raise funds to conduct preclinical and early-phase clinical trials, covering the high costs of Phase III trials and FDA approval has, thus far, remained an insurmountable challenge without the involvement of larger biopharmaceutical partners.

The subgroup discussed opportunities and challenges for nonprofit entities, [public benefit corporations \(PBCs\)](#), government-backed initiatives, and mixing of models. Members also discussed sources of funding, such as philanthropic donations, social impact investments, and government funding agencies. We took specific interest in genetic therapies for [rare and ultra-rare diseases](#) where there is a failure of the traditional commercial model to translate approved products and where clinical trials are typically smaller and less expensive to orchestrate administratively. Importantly, the goal of our discussions was not to propose a replacement of the existing for-profit/venture capital framework, but to conceive of sustainable complementary models.

### Recommendations

Given the complexity of each stage of development and the need for specialized expertise, we recommend an organizational model that distributes key responsibilities and activities across mission-aligned players who have the ability to leverage various sources of funding.

- An academic institution can leverage government and philanthropic funds to drive discovery research and conduct early preclinical studies.
- Intellectual property (IP) rights could be transferred to a 501(c)(3) nonprofit organization that can leverage its tax-exempt status to effectively draw on philanthropic donations. The nonprofit should have the necessary expertise to conduct clinical trials and engage with the FDA. It would also hold any BLAs.
- A public benefit corporation should be established to manufacture and distribute the genetic therapy. As a for-profit entity, it has the capacity to take low-to-moderate cost capital, or traditional venture capital if profits are sufficient. It would also pay licensing fees to the nonprofit organization to help sustain its operations.
- Well-defined governance structures between the separate legal entities are absolutely essential. Both the nonprofit and public benefit corporation should be set up with governance provisions in their charters that assure the intended public benefit when licensing agreements are negotiated.

### Nonprofit organizational models

#### 501(c)(3)

Most nonprofit organizations fall under the umbrella of “501(c)(3) charitable organizations”, including those with religious, educational, scientific, and charitable purposes. They are typically funded through government grants, member fees, fee-for-service, contributions, and donations, which are tax-exempt. To qualify as a public charity, one third of all donations must be derived from the public rather than any one donor (also referred to as the “public support

test”), and individuals and shareholders cannot gain financially from the net earnings. Political and legislative work by a 501(c)(3) are also limited.<sup>99,100</sup>

In the US, pharmaceutical companies that have been awarded 501(c)(3) designation are subject to review within seven years of formation, which has resulted in challenges to retain their nonprofit status. The Internal Revenue Service has been reluctant to approve tax-exempt status for pharmaceutical manufacturing organizations and, in some cases, has done so on the condition that the entity provides the majority of its product to the public below cost - a financially unsustainable business model. The laws governing nonprofit organizations differ globally. For example, the world’s wealthiest charitable organization, the Denmark-based Novo Nordisk Foundation, has corporate interests and owns the Novo Nordisk pharmaceutical company. Denmark also boasts the Lundbeck Foundation, a nonprofit foundation focused on brain health. The breadth of these two organizations are enabled by Danish law.

While uncommon, there are examples of 501(c)(3) organizations in the pharmaceutical and drug development space including Caring Cross (Box 4), Odylia Therapeutics (Box 5), Medicines360<sup>101</sup>, or France-based Généthon<sup>102</sup>. One of the main issues that nonprofit organizations attempting to develop, manufacture, and deliver therapies face is raising enough capital to sustainably fund operations, particularly over a long development period and before they start generating revenues. In Europe, a recent consortium effort, known as Access to Gene Therapies for Rare Diseases (AGORA), brings together key stakeholders and experts in hopes of addressing commercialization challenges by supporting academic and nonprofit programs as they seek regulatory approval and harmonizing national activities across the continent.<sup>103,104</sup>



### Medical research organization

A medical research organization (MRO) is a special type of 501(c)(3) public charity which must either invest more than 50% of its assets or over 3.5% of the fair market value of its endowment in active research, assessed over a seven year period (Treas. Reg. § 1.170A-9(d)(2)(iv) and § 1.170A-9(d)(2)(v)(B)). As an asset moves from development to FDA approval, the entity will need to shift its business operations to commercializing a pharmaceutical product, while also balancing its research obligations.<sup>105</sup> This shift to commercialization is further challenged by IRS-imposed limits on commercial sales of a product by a nonprofit. Under these IRS limits the majority of products would have to be provided for free, making product commercialization unsustainable for the nonprofit.

### 501(c)(4)

There are two types of 501(c)(4) organizations with distinct requirements, social welfare organizations and local associations of employees.<sup>106</sup> For the purposes of this report, we will focus on social welfare organizations. Similar to 501(c)(3) entities, 501(c)(4) organizations cannot benefit an individual or private shareholder and their operations must exclusively address their specific social welfare mission. Key differences include that donations to 501(c)(4)s are not tax-deductible and that these entities are permitted to be politically active. 501(c)(3) organizations may choose to also have a 501(c)(4) arm or vice versa to expand permissible activities; however, that requires more meticulous bookkeeping.<sup>107,108</sup> Civica Rx, a generic drug company, is an example of a social welfare organization in the pharmaceutical space ([Box 7](#)).

### Box 4. Caring Cross, a nonprofit 501(c)(3)

Caring Cross is a developer of advanced medicines with a mission to ensure broad access to its drugs by supporting healthcare professionals, scientists, engineers, community advocates, and business leaders. The nonprofit is focused on developing place-of-care manufacturing for cell and gene therapies within local hospitals, clinics, and healthcare organizations globally. They are funded by a combination of grants, contracts, and through public-private partnerships such as the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL).

Caring Cross has created standards for the field of gene therapy with regard to vector manufacturing and has published open source protocols and procedures that may help start-ups standardize their processes, something for-profit organizations are disincentivized to do. Caring Cross has also negotiated contracts with private entities for research services using its in-house expertise. These agreements are non-exclusive and ensure that the nonprofit has freedom to operate in LMICs.

Recently, Caring Cross financed its first company, Vector BioMed, a public benefit corporation that will serve the market as a [Contract Development and Manufacturing Organization \(CDMO\)](#) for lentiviral gene vector manufacturing. Caring Cross plans to establish public benefit companies with the goal of making essential, GMP-compliant components like lentiviral vectors affordable for projects in LMICs, such as CAR-T therapies for HIV and leukemia or engineering of bone marrow stem cells to treat sickle cell disease. To do this, each public benefit corporation would commit in its charter a specified percentage of production capacity to Caring Cross as well as preferred pricing.

### Box 5. Odylia Therapeutics a nonprofit 501(c)(3) developing gene therapy

Odylia Therapeutics is an organization focused on accelerating drug development for rare diseases by combining philanthropy, strategic planning, and innovative industry partnerships. Founded in 2017, Odylia receives its funding through a combination of philanthropic support, fee-for-service consulting, and licensing and milestone revenue. Having been seeded with an exclusive sublicense for a novel AAV vector (Anc80), discovered in the lab of Luk H. Vandenberghe, the organization is able to generate revenue to fund the next generation of targets in its pipeline through out-licensing and co-development opportunities. As the nonprofit has obtained a Rare Pediatric Disease Designation for its lead program, additional funds could be raised through the sale of a [priority review voucher](#) in the future. Odylia has also established strategic partnerships for each of its gene therapy programs. The nonprofit further leverages its expertise in the rare disease space by offering scientific guidance and project execution services through the Brydge Solutions program, furthering the mission to accelerate therapeutic development for rare diseases.

Odylia is currently developing gene therapies to treat two rare disorders of vision loss caused by mutations in the *RPGRIP1* and *USH1C* genes. Its preclinical stage gene therapy programs are advanced through a network of global academic leaders, patient groups, industry partners, and philanthropic donors. Odylia works to de-risk these programs such that they will attract industry interest and investment (usually at an early clinical stage).

#### Key considerations for tax-exempt organizations

While nonprofit organizations provide a crucial mission-driven alternative to for-profits, a number of factors should be taken into account before deciding on this structure for the purposes of drug development and distribution/commercialization. Sustainability of an organization is a key concern that Task Force members raised repeatedly, as success depends upon raising sufficient funds, recruiting and retaining talent, and consistently accessing supply chains.

In 2019, Waxman Strategies published a white paper<sup>105</sup> that highlighted several key challenges in addition to those that were already mentioned:

1. The amounts of funding required to research, develop, manufacture, and market a drug can pose a significant challenge to a nonprofit meeting the public support test to show diverse revenue streams from a broad base of donors.<sup>109</sup>
2. FDA user fees, charged to cover the cost of the agency's pre- and post-market activities, are high and set irrespective of a user entity's mission or sales.<sup>110</sup> There are some waivers for rare diseases or orphan drug designations.<sup>111</sup>
3. Nonprofit organizations cannot take advantage of some federal grant programs, such as the Small Business Innovation Research (SBIR) program, and may further be ineligible for state funding for research and development (R&D).
4. Talent recruitment and retention can be a challenge due to limited operating budgets to cover salaries and the absence of stock options as additional compensation.

Depending on the specific circumstances, some nonprofit organizations will be less impacted by these challenges than others. Additionally, there are unique benefits to nonprofits that should not be discounted, such as their tax-exempt status, greater public trust<sup>112</sup>, access to specific grants, discounts or alternative fee structures, ability to attract mission-aligned workforce and in-kind contributions, and philanthropic support. It is crucial to plan ahead and evaluate the suitability of the nonprofit model on a case-by-case basis.

### Public benefit corporations

As nonprofit organizations have requirements on their sources of funding and encounter unique challenges in the pharmaceutical space, and for-profit corporations are bound by an obligation to maximize shareholder value, an intermediary form has emerged -- the public benefit corporation (PBC).

The PBC model, first introduced in 2010 in Maryland<sup>113</sup>, establishes a type of corporate framework that must produce a general public benefit, be transparent, and meet additional accountability criteria. Like C corporations, PBCs pay the same rate of corporate taxes and must report successes and failures to their shareholders annually. Importantly, PBCs have the ability to make decisions based on explicit non-financial goals and their obligation to shareholders without facing the risk of legal action. This ability has been referred to as a “triple-bottom-line” approach to business, with focus on people, planet, and profits.<sup>114–116</sup> While we describe one example of a PBC in [Box 6](#), more information and additional examples of pharmaceutical PBCs can be found in a recent research synthesis article from The Geneva Graduate Institute.<sup>117</sup>

### Box 6. The Mark Cuban Cost Plus Drug Company, a public benefit corporation providing drugs at acquisition cost plus transparent markup and shipping fees

The Mark Cuban Cost Plus Drug Company (MCCPDC; Cost Plus Drugs) is a public benefit corporation providing low-cost generic drugs, financed by billionaire entrepreneur Mark Cuban.<sup>119,120</sup>

Cost Plus Drugs is able to offer ~1,000 mostly generic drugs by purchasing them directly from manufacturers and side-stepping pharmacy benefits managers who typically negotiate drug prices. The cost of drugs at MCCPDC is determined by the price negotiated directly with the wholesale manufacturer plus a 15% markup and \$8 in labor and shipping fees.

As this venture is still relatively new (started in January 2022), it remains to be seen whether it can effectively reduce drug prices in the long-term. The company’s effect on the pharmaceutical industry will be limited, as nearly 80% of pharmaceutical industry revenue is made on brand-name drugs, not generics. Nonetheless, experts see benefits to uninsured, underinsured, and underserved populations, especially as MCCPDC’s manufacturing capacity expands.<sup>121,122</sup> While most patients will still need to pay for drugs from the MCCPDC out of pocket, the company has started to partner with health plans.<sup>123</sup>

### **Key considerations for Public Benefit Corporations**

Positioned between mission-driven and profit-driven organizations, PBCs share some of the advantages and drawbacks of both. While they pay the same tax rates as traditional for-profit corporations and have more onerous reporting requirements, PBCs can draw on more diverse sources of revenue, potentially attracting unique sets of investors, and enjoy limited liability and tax deductions. Transparently working towards a defined public benefit can build trust and broaden the customer base, while also bringing in profits that ensure sustainability and help recruit mission-oriented talent. It is noteworthy, however, that shareholders will likely have to contend with less profits in pursuit of the mission.<sup>118</sup>

### **Government-backed efforts**

Even in high-income countries, governments with publicly funded healthcare systems weigh providing access to available therapies against funds to cover government expenditures. With the number of indications expected to be treatable with genetic therapies growing rapidly, disagreements between drug manufacturers and governments on prices, such as that between Bluebird Bio and the European Union on the cost of Zynteglo<sup>124</sup>, appear more likely. Alternatives to reliance on commercially available products are being explored by a number of countries. The COVID-19 pandemic has highlighted the dependence on international supply chains and brought urgency to the expansion of domestic [Good Manufacturing Practice \(GMP\)](#) manufacturing capacity for vaccines and other biologics. In Brazil, for example, there is a long-standing state policy for the public production of medicines (including biologics) and vaccines, mostly through Biomanguinhos and Instituto Butantan, both government owned ([Box 2](#)).<sup>125</sup> As discussed in [4. Manufacturing and Regulation](#), an important example of government-backed efforts

to advance affordable and accessible genetic therapies is the made-in-Canada point-of-care model implemented by BioCanRx ([Box 1](#)).

### **Key considerations for publicly funded ventures**

There are a number of factors that can influence the success of government-supported pharmaceutical manufacturing. Incidentally, the primary cost driver for manufacturing is the high cost of compliance with regulations where government grants are insufficient to cover the full cost of drug approval. Government backed efforts could be accompanied by a regulatory support component to lower the cost of supported products. Regulators in the US, Canada, and the EU have all initiated programs to provide regulatory guidance on manufacturing (including distributed manufacturing), and some have provided additional financial support to nonprofit developers of cell and gene therapies.<sup>70,126–128</sup>

### **Mixed models**

To successfully navigate all aspects of therapeutic development, including raising capital, completing regulatory processes, and product manufacturing, a group of affiliated organizations with separate responsibilities and distinct expertise may be most suitable. Such a “mixed model” has been successfully employed in the pharmaceutical space. For example, Medicines360, a nonprofit MRO distributes and commercializes its products through its subsidiaries ImpactRH360 (a limited liability company that distributes globally) and Curae Pharma360 Inc. (a for-profit that commercializes and distributes in the US). Similarly, Civica Rx (a 501(c)(4)), which was created to address drug shortages, established the 501(c)(3) Civica Foundation to be able to receive philanthropic donations, as well as the PBC CivicaScript to lower the cost of targeted generic drugs for

consumers in the retail pharmacy setting (Box 7). In these cases governance structures are important considerations in order to maintain public benefit requirements from the nonprofit to the for-profit entity.

### Funding models

One key question is of course how to finance an economically sustainable venture. A new pharmaceutical organization requires significant upfront investment, which, if it aims to keep prices affordable, needs to be secured at a lower rate of return. As such, an initiative focused on affordability rather than profit maximization is unlikely to attract traditional venture capital investors and will need to look to alternative sources of capital.

Organizing capital for public benefit purposes is a known issue impacting all pharmaceutical fields. Recently, a new nonprofit, the 90/10

Institute, formed that is dedicated to innovative ways to finance the public benefit pharmaceutical industry. Some characteristics of the financing terms that would better align with the purpose of public benefit pharmaceutical companies are:

- Capital seeking long range (10+ years), regularly distributed, moderate returns
- A continuum of capital structures/vehicles that can sustain companies from early to mature stages
- The potential to accept capital that does not require a return on investment (such as government and philanthropic grants)
- Support for development of repurposed as well as novel products

### No-cost capital - gifts and grants

Philanthropic donations, such as those from foundations and charitable organizations, and grants from public institutions are the cheapest

### Box 7. Civica Inc. (Civica Rx, Civica) is a nonprofit generic drug company with a mixed organizational model

Civica Rx was established by seven US health systems and three philanthropies to address the problem of drug shortages - a longstanding failure of the traditional pharmaceutical sector to reliably supply essential medicines. Civica was launched in 2018 as a non-stock, nonprofit 501(c)(4) social welfare organization based on four principles: the company has no owner and is managed by “stewards”; all purchasers pay the same price with no hidden rebates or off-invoice discounts; large-scale operation to achieve financial sustainability; and initial capitalization of the enterprise provided by the hospital buyers. This model has been described as a “health care utility”.<sup>129</sup> The nonprofit currently serves more than 55 health systems, accounting for one in three US hospital beds, and has delivered more than 100M containers of 70 different drug products.

Civica expanded its mission through the establishment of CivicaScript, a PBC focused on lowering costs for consumers. CivicaScript was established in part due to the challenges that nonprofit pharmaceutical companies have encountered with obtaining IRS recognition. CivicaScript, another health care utility, was formed in partnership with 18 Blue Cross and Blue Shield health plans. Civica has also established a 501(c)(3) supporting foundation, the Civica Foundation, which enables philanthropic giving to support the development of quality, affordable medications. In March 2023, Civica announced entering into a \$50M contract with the state of California to produce insulin under the state’s brand name, CalRx, in an effort to reduce and stabilize the price of the drug. The organization announced it would charge no more than \$30 per vial.<sup>130</sup>

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form of capital as they do not require repayment. Most research grants for basic and pre-clinical innovation for cell and gene therapies are awarded by the National Institutes of Health (NIH). However, NIH grants are primarily focused on early-stage research and translational projects rather than large and costly late-stage clinical trials.<sup>97</sup>

In March 2022, the Advanced Research Projects Agency for Health (ARPA-H) was established to complement NIH funding, and has been appropriated \$2.5B as of early 2023.<sup>131</sup> ARPA-H will occupy a niche of supporting high-risk, high-reward research projects that fall in the gaps between academia and the biopharmaceutical industry, including areas where the near-term market opportunities are too small for commercial investment.<sup>132</sup> While specific research priorities for ARPA-H have yet to be announced, its website suggests that tackling issues of scale to achieve equitable solutions is a main focus.<sup>133</sup>

In order to fill the translational research gap, several states also have dedicated funds for special health research projects. For example, the California Institute of Regenerative Medicine (CIRM) is a state agency authorized to receive \$8.5B from bond sales to advance stem cell research.<sup>49–51</sup> It has \$4.1 billion left for future awards. In Texas, voters have approved a total of \$6B in state investment to fund the Cancer Prevention and Research Institute of Texas. These grants fund research into the causes of human cancers, cancer prevention programs, infrastructure expansion, and the development of cancer treatments and cures, including cellular immunotherapies.<sup>134</sup>

Federal and state tax credits, while indirect ways to raise funds, can have added benefits to a tax-liable entity. In the US, the R&D tax credit, also known as Research and Experimentation tax credit, was established in 1981 to drive

innovation in a number of areas, ranging from agriculture to software development.<sup>135</sup> The final tax credit is a percentage of Qualifying Research Expenses which include wages, supplies, and “contract research expenses”.<sup>136,137</sup> A large number of states offer additional R&D tax credits, including California, Texas, Massachusetts, New York, and Illinois.<sup>138</sup>

The potentially outsized impacts of philanthropy to advance new medicines are increasingly being recognized. The Milken Institute’s Center for Strategic Philanthropy, which advises philanthropists and foundations on targeted giving, recently highlighted the challenges to raise funds to conduct clinical trials for rare disease therapeutics in a guide to medical philanthropists.<sup>139,140</sup>

Advocacy groups for specific disease indications may also fundraise for basic, translational, and clinical research studies and collect royalty revenues. Examples include the Cystic Fibrosis Foundation and the Rett Syndrome Research Trust. More unconventional funding may also be raised through crowd-funding, though the scale may be small and better suited to cover operational costs than those of R&D.

An organization built solely on grant and philanthropic funding is unlikely to be viable in the long run, requiring extreme amounts of fundraising in perpetuity. However, if startup or early R&D costs are funded by low-to-no cost capital it could enable the entity to become established and be self-sustaining in the long term.

### **Low-to-moderate cost capital - Social impact funding**

Social impact investors seek to address challenges faced by people and the planet while also obtaining financial returns typically below market rate. Defining and measuring impacts and outcomes are key to accountability, a pillar of social impact investing.<sup>141</sup> Venture philanthropy follows a similar model, developed by venture capitalists who typically provide grants to nonprofit organizations with the expectation of a return only if valuable intellectual property has been generated, or a profit is made. This conditional return on investment is less burdensome to the nonprofit or company.

Social impact bonds are a type of social impact investing in which high-quality public services are achieved by public-private partnerships. Private capital serves to improve social outcomes and the associated cost-savings are used to repay investors. A key distinguishing feature of social impact bonds is that principal repayment and return on investment are only required if the project attains its stated social outcomes.<sup>142,143</sup>

Philanthropic foundations can also offer money to mission-aligned entities in the form of Program-Related Investments. Examples include low-interest loans to underprivileged students and investments in nonprofit affordable housing projects. These investments can be a low-cost source of capital, often with below-market interest rates.<sup>144</sup>

Another proposal to help mitigate the impacts of clinical trial costs is a government-backed loan program. H.R. 3437, the Long-term Opportunities for Advancing New Studies (LOANS) for Biomedical Research Act<sup>145</sup>, was introduced in the 117th Congress (2021-2022), but did not move. This bill would have required HHS to guarantee “BioBonds” as a loan mechanism to fund FDA-

approved clinical trials for drugs or devices intended to address an unmet medical need.<sup>146</sup>

The goal of BioBonds is for the US government to provide limited guarantees for equity investors in clinical research, similar to government guarantees to private lenders of mortgage loans.

Others have proposed more sophisticated financial instruments, including pharmaceutical organizations issuing debt and bundling several biomedical programs into one megafund to spread risk.<sup>147</sup> The idea of backstop capital has also been proposed where philanthropic funding is the first money loss, reducing risk for private investors.<sup>148</sup>

### **Internally generated funding**

In order to support expensive R&D, an entity could generate revenue from its assets such as licensing IP to generate royalties. Entities can further generate income by offering expertise or infrastructure capacity. For example, manufacturing services could be offered to produce Phase I-GMP-compliant batches of a novel therapeutic for testing. Similarly, project design and implementation expertise can be offered as consulting services.

Forming partnerships with other mission-aligned organizations can also reduce cost or raise revenue. For example, an entity closely aligned with a research institution may be able to test its therapeutic candidates in a preclinical setting in exchange for a discounted price for a service.

The sale of [Priority Review Vouchers \(PRVs\)](#) can provide a substantial influx of funds. PRVs were established as an incentive for companies to develop treatments for designated rare, pediatric, or tropical diseases. Upon approval of such a therapeutic, FDA will award a PRV which can then be sold on an open exchange to a pharmaceutical company. A PRV can reduce

## ORGANIZATION AND FUNDING MODELS

the time to review a New Drug Application or Biologics License Application to six months. In recent years, PRVs have sold in the \$110M range.

Lastly, once an entity has sales revenues, they can be used to support further R&D and regulatory approval, especially of commercially non-viable therapies. A diversified portfolio is thus critical to ensuring long-term sustainability.

### Innovation in funding

While we outline some potential funding options, innovation in funding is desperately needed and could include a federal level bond mechanism similar to CIRM. Task Force members also proposed leveraging the joint buying power of insurance companies. For example, if insurance companies invested earlier in the process to fund manufacturing scale-up for guaranteed lower prices, this could be a win-win (see example in [Box 7](#)). However, such an approach would be difficult to implement for public [payers](#) like the Centers for Medicare and Medicaid Services who have strict laws restricting what they can pay for.

### Example organizational and funding model

Considering the benefits and pitfalls of each organizational model, we illustrate how an academic institution might bring a genetic therapy to market outside of the traditional for-profit/venture capital structure. We recommend a framework that divides responsibilities based on access to different types of funding and the need for varied expertise ([Figure 3](#)). Broadly, an academic institution would drive the research, an MRO would be in charge of clinical trials management and communication with the FDA, and a PBC would oversee product manufacture and commercialization/distribution.

Academic institutions are best positioned to obtain NIH and philanthropic funding for investigations of disease mechanisms, proof-of-concept studies in

preclinical models, and therapeutic development. If the academic institution's technology transfer office is aligned on affordability and access goals, IP could be transferred to the 501(c)(3) MRO under favorable conditions.

A nonprofit is able to leverage tax-deductible foundation grants and philanthropic donations to commence operations and hire the necessary expertise. The MRO would, among other duties, handle FDA filings, manage or outsource clinical trials, oversee commercial contracts, and ultimately hold the BLA of any approved genetic therapy to retain long-term control of its assets. Should a priority review voucher be awarded based on the disease indication, the MRO could sell it and use the funds to pursue additional clinical studies. Of note, Task Force members specifically advise keeping these functions separate from the academic institution as the professional skill sets needed to run professional clinical trials are distinct from those commonly found in academia. Moreover, it may be challenging for public institutions to recruit and retain the necessary expertise if pay restrictions foreclose industry-level compensation.

Lastly, the PBC would manufacture, sell, and distribute the product. The price of the genetic therapy would be anchored in the [cost of goods](#) and labor, i.e., a dynamic cost-plus approach as outlined in [3. Pricing and Access](#). To build capacity and hire staff, the PBC could raise capital from venture philanthropy, bonds, loans, and traditional venture capital. It could also generate profits by offering its manufacturing services to outside organizations. Alternatively, manufacturing could be contracted out, if financially prudent. The PBC will need to pay licensing fees to the MRO, which the nonprofit can use to sustain itself.

The governance structures of different legal entities are critically important in order to maintain public benefit. However, mission alignment should be



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built into each organization's charter to ensure continued values convergence. In this model, the 501(c)(3) and PBC are separate legal entities with separate - though potentially overlapping - Boards of Directors. Overlapping directorates would assure that the organizations make coordination a top priority. The MRO should be set up with governance provisions to disincentivize profit motives and to ensure that its technology is licensed in a way that assures public benefit. Because the MRO controls the IP they will be able to decide on what types of therapies to prioritize ex. most likely to reach the public or largest population.

### Conclusion

In order to lower the cost of genetic therapies we suggest that a public benefit corporation or mixed model are fit for purpose, as they mimic existing approaches that have been proven to

work, but with different incentives and legal protections that permit the pursuit of societal benefit. While an unlikely path in the US, in countries with socialized healthcare systems government-funded or operated models can work well. A key consideration to achieve affordable genetic therapies is the cost of capital. While social impact investment is slowly moving into the mainstream, traditional expectations of very high returns in the pharmaceutical space necessitate further innovation, such as government bonds or loan programs. As the tremendous potential of genetic therapies to cure currently intractable diseases is realized, novel business solutions are urgently needed to ensure the benefits of biomedical discoveries are shared equitably. New models will spur innovation and competition that will undoubtedly benefit people.

### Proposed Organizational Model

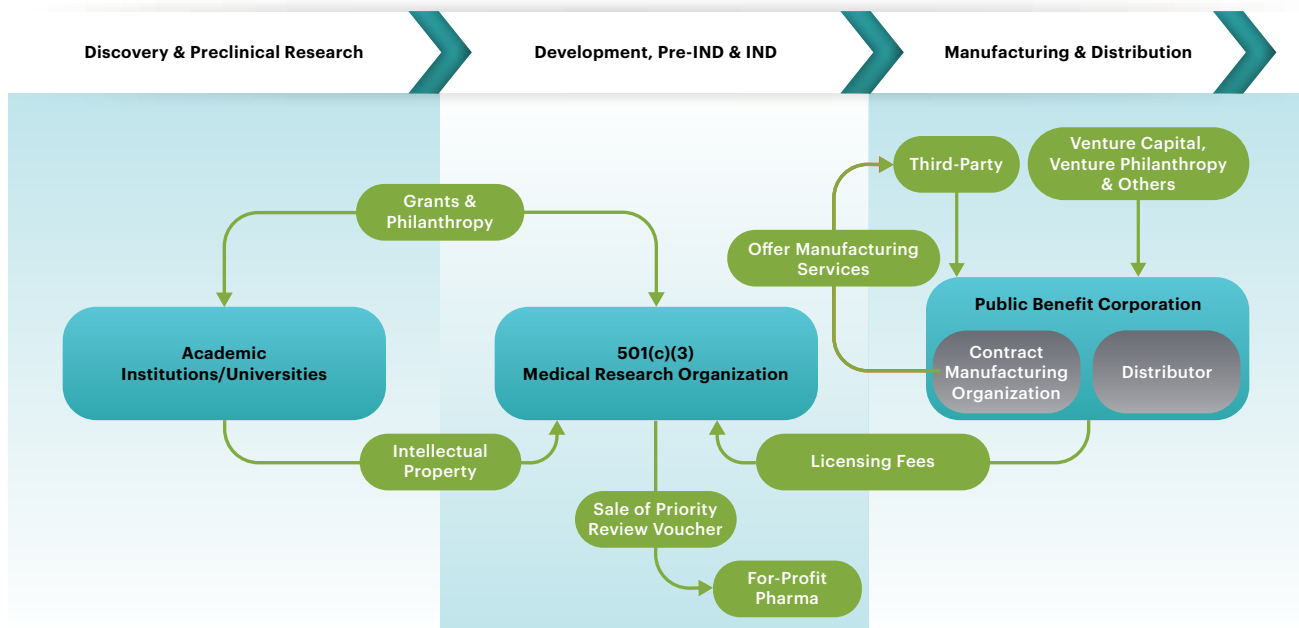


Figure 3: A proposed mixed organizational model to develop a cellular or genetic therapy. A nonprofit conducts R&D using philanthropic or government funding that requires no, or low, return on investment. An MRO further develops and translates the product through clinical trials and a public benefit corporation would manufacture and distribute the product on a financially self-sustaining basis.

## 7. POLICY RECOMMENDATIONS

While the Task Force primarily focused on ways to reduce the price of a [genetic therapy](#), we also considered policy changes that would promote the entry to market of lower-cost therapies.

Below we provide a non-exhaustive summary of the current policy landscape and highlight recommendations made by Task Force members.

1. The Department of Health and Human Services is testing The Cell and Gene Therapy Access Model, under which the Centers for Medicare and Medicaid Services (CMS) would administer multi-state, outcomes-based agreements with biopharmaceutical manufacturers on behalf of state Medicaid agencies in order for beneficiaries to access certain cell and gene therapies.<sup>149</sup> However, the success of any such arrangement will hinge on establishing measurable and meaningful clinical outcomes, which can be extremely difficult to ascertain in a timely manner for gene therapies.

**Recommendation:** Implementing a model that aggregates demand among state Medicaid agencies would increase the negotiating power of CMS to help bring down costs and expand access to transformative treatments. The FDA should require manufacturers to collect further evidence through clinical trials or observational studies, which would yield important and critical insight into the long-term safety and efficacy of treatments. Medicaid could reduce reimbursement by X% until manufacturers confirm clinical benefit, then provide retroactive benefit in Y years.

2. Insurers can cover expensive medical treatments through reinsurance. However, there is some concern that genetic therapies will be excluded by the private reinsurance

market if they are too costly. The Affordable Care Act (ACA) includes reinsurance provisions for plans that cover high-cost individuals.<sup>150</sup>

**Recommendation:** The ACA reinsurance provisions could be expanded to explicitly include coverage of genetic therapies, potentially incentivizing private insurers to offer coverage with fewer barriers.

3. The FDA is making clear strides towards clarifying and/or developing new policies to support lower cost drug manufacturing.

**Recommendation:** The FDA should develop guidance for point-of-care manufacturing to facilitate point-of-care infrastructure development and use.<sup>70</sup> Greater regulatory clarity is needed regarding phase-appropriate [CMC](#) requirements for critical raw materials and for development of platform approval procedures

4. Current IRS limits on the activities of nonprofit pharmaceutical companies as well as government limitations on access to government [funding](#) make it difficult for non-traditional pharmaceutical organizations to deliver public benefit.<sup>105</sup>

**Recommendation:** Congress should establish a specific IRS designation for nonprofit pharmaceutical manufacturing entities. Nonprofit entities, such as MROs, that meet all the tests to be small businesses based on revenue and employment data should be made eligible to receive Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants. Policies should ensure prices set by an organization are transparent and appropriate if they are brought to market using organizational structures and funds dedicated to enhancing affordability and access.

## POLICY RECOMMENDATIONS

5. The Consolidated Appropriations Act, 2023 calls on the Government Accountability Office to prepare a report on nonprofit pharmaceutical manufacturers and their role in lowering prescription drugs (Pub.L. 117-328 § 3207). In the same budget bill, the Department of Health and Human Services is tasked with conducting a feasibility study on increasing domestic production of generic medicines through nonprofit and for-profit organizations (Pub.L. 117-328 § 2410).

**Recommendation:** As lawmakers become more aware of the role entities that are not (exclusively) profit driven play in making therapies more affordable and accessible, [academic institutions](#) should actively participate and offer their relevant expertise in the development of government planning documents and reports.

6. In many cases therapies for ultra rare disorders will never be commercially viable, even if they are shown to be effective.

**Recommendation:** Lawmakers and regulators could create supportive regulatory structures that allow academic facilities to continue to treat patients under similar protocols and [GMP](#) requirements as those for early Phase clinical trials. These policies would allow effective treatments to continue in academic facilities for those with ultra rare disorders.

## 8. CONCLUSIONS

Throughout this report we provide detailed landscape and situational assessment accompanied by recommendations for [academic institutions](#) that improve the affordability and access of [genetic therapies](#) that originate in their labs. In some cases these recommendations work together in concert, while in others they may be singular actions that organizations can take to improve access. In order to address the complementarity and coherence across recommendations in the report we provide a couple hypothetical scenarios that integrate multiple recommendations.

### **Hypothetical scenario 1:**

#### **A utopian public benefit company model**

It's the year 2030, and a [public benefit corporation](#) named Eleemosynary, which was launched in 2022, received start-up [funding](#) from several venture philanthropists, federal grants, a patient advocacy foundation, and through an expanded pool of funding from state and federal funding agencies. The company has had considerable difficulty raising capital because they are unattractive to traditional VC firms given their focus on affordability.

The funding agency, recognizing manufacturing and regulations as a key bottleneck, decided to provide half the funding necessary (\$50M) to build a manufacturing facility that explicitly promotes access and affordability and bolsters production capacity of prior grantees. In the preceding eight years the [Food and Drug Administration \(FDA\)](#) has gained experience regulating genetic therapies and has lowered some regulatory barriers to manufacturing (through stakeholder consultations and additional safety data), significantly smoothing the way for Eleemosynary to complete building of the manufacturing facility.

Eleemosynary licensed a significant patent portfolio from a major university that includes the core technology for a [rare disease](#) therapy that has successfully completed Phase III clinical trials– which were paid for by a patient advocate foundation. Eleemosynary has also licensed the technology to treat an ultra-rare disorder that affects fewer than 100 people per year in the US and which has completed Phase II clinical trials. There are currently two different therapies for the rare disease on the market, one costing \$3M and another costing \$2.1M, although there are reports that one of the companies will lower their therapy to \$1.8M to reflect the new competitive landscape. Both drugs have been used to treat hundreds of [patients](#) in the US who can afford the therapy, most of whom are privately insured, increasing societal and patient confidence, and making it easier for Eleemosynary to enter the market.

Eleemosynary negotiates a contract with a [center of excellence](#), the new CMS cell and gene therapy access pool, and a major insurer to provide the doses at an average of \$320,000 per patient. This contract guarantees a customer base and provides some additional funding for manufacturing from the private insurer. There are ~200,000 patients with the disorder in the US, and several million globally. Eleemosynary plans to produce 2,000 doses per year for the rare disease therapy. At this price and number of patients treated, they estimate that they will be cash flow positive in about three years and can begin to pay investors at moderate gains. They also hope to use excess capital to produce the 100 doses per year for the ultra-rare disorder in the same facility. Although the ultra-rare disorder treatment still needs to undergo Phase III clinical trials and is money losing, they can provide doses under their public benefit mission.

### **Hypothetical scenario 2: Intellectual property rights for LMICs**

In 2026, a Phase I/II clinical trial for sickle cell disease (SCD) has just been completed and has shown a promising safety profile. The university system that completed the clinical trials is approached by a for-profit company, seeking to license its technology. While the university exclusively licenses to the company in the US, they indicate that university researchers plus collaborators would like to develop the technology in Brazil. The university negotiates with the company to ensure that they will register and make the core technology available to treat people with SCD in Brazil, estimated at ~100,000 people. The sponsors hope that positive outcomes in Brazil would impact the path to approval in other countries with substantial SCD burden, such as India.

In collaboration with a large hospital and research ecosystem in Brazil, the university has helped to expand manufacturing capacity to 1,000 doses per year. Partnerships with over 70 hospitals enable patient access across the country, with the greatest prevalence of SCD in its northeastern regions (1 in 650 people). The Brazilian government operates the country's health insurance system and is incentivized to smooth the regulatory pathway for point-of-care manufacturing, further lowering costs.

Start-up funding was provided by philanthropic donations but the effort is partially maintained by the Brazilian government. There is a concern about sustainability of the effort in the long-run as they are quickly spending the initial philanthropic funding. Manufacturing each dose is estimated to cost \$100,000 and the Brazilian government only covers ~\$50,000. While still extremely expensive, it is cost-effective long-term, considering that it costs ~\$2,000/year for a lifetime to treat each SCD patient using the standard of care. There are hopes that the success of the program will attract further philanthropic funding, or that costs can be lowered through technological improvements to ensure sustainability.

While both of these examples assume that some of the key drivers of cost will improve (such as regulatory and manufacturing hurdles) and that there will be some availability of government and philanthropic funding, we hope they illustrate how these ideas may be implemented in concert in the near future.

# 9. APPENDICES

## APPENDIX I: DEFINITIONS

### **Academic Institutions**

Entities dedicated to education and research that span multiple disciplines, generating biological discoveries with therapeutic potential. Academic institutions can translate research into approved therapies by licensing IP to private sector partners through university TTOs, or may choose to carry out clinical testing in-house using multidisciplinary project teams. Institutions may collaborate or contract out specific functions (e.g., regulatory advising, manufacturing) depending on their capacity and expertise.

### **Allogeneic and Autologous Cell Therapies**

The primary difference between allogeneic and autologous cell therapies is the source of the cells for the therapy. Allogeneic cells, sometimes referred to as “off-the-shelf,” are manufactured in large batches, use cells from matched related or unrelated donors, and can be used to treat many patients. Autologous cells are “custom” products that use the patient’s own cells, minimizing potential immune responses, and are sometimes manufactured on site at the clinic or hospital.

### **Biologics License Application (BLA)**

Usually submitted after IND approval, a BLA is a request to the FDA for permission to distribute a biologic across state lines. The equivalent of a BLA for a non-biologic drug is referred to as a New Drug Application (NDA).

### **Care Providers**

Facilities (e.g., hospitals, clinics, centers of excellence) licensed to provide diagnosis and treatment services, and often receiving payments in return from health insurance providers.

### **Center of Excellence (COE)**

A type of care provider, often within larger healthcare facilities, with highly skilled and multidisciplinary teams of experts dedicated to a specific therapeutic area and/or provide highly specialized and comprehensive treatments and procedures for complex conditions. COEs also provide leadership and best practices and can be hubs of clinical research.

### **Chemistry, Manufacturing, and Controls (CMC)**

Describes a set of processes that ensures product safety and consistency between batches, used across the full cycle from clinical development to commercial scale production. CMC is included in IND applications, addressing manufacturing practices and product specifications such as quality, stability, and strength.

### **Contract Development and Manufacturing Organization (CDMO)**

A company that provides development and manufacturing services on a large scale. CDMOs help transition smaller-scale, research-grade materials and procedures into industrial manufacturing processes that use Good Manufacturing Practices. CDMOs also offer regulatory strategy and technical support, and can increase cost effectiveness and accelerate market access by centralizing expertise and infrastructure.

### **Contract Research Organizations (CRO)**

A company that provides private sector drug developers and academic institutions with outsourced research services, including clinical development, clinical trial management, and outcomes research. CRO services are primarily applied to the early stages of the drug development pipeline, including R&D and clinical trials, while CDMO services are often used downstream prior to or during commercial phases.

### **Cost of Goods (COGs)**

The summation of direct costs, which include labor, materials, and third party services (cell transportation) and indirect costs, which include overhead costs such as facility costs and management. COGs may also include non recurring investments (e.g., establishing a GMP facility) and the cost of failed manufacturing lots. COGs can significantly vary depending on the delivery vehicle (e.g., AAV vs. lipid nanoparticles), cell manufacturing approach (e.g., allogeneic vs. autologous), the use of automated machinery, or the outsourcing of processes.

### **Food and Drug Administration (FDA)**

A US federal agency, within the Department of Health and Human Services, that is responsible for protecting public health by ensuring the safety, efficacy, and security of human drugs, biological products, and medical devices. The FDA ensures that the design, implementation, analysis, and reporting of clinical trials adheres to Good Clinical Practices (GCP) regulations and federal law. Within the FDA, the Center for Biologics Evaluation and Research (CBER) regulates cell and gene therapy products and related devices.

### **Funders**

A person or organization that provides money for particular purposes and with certain motivations and incentives. Philanthropic and government funders, often motivated to maximize positive societal impact, are key drivers of academic research and may also help support early-stage clinical testing. While venture capital funding or investments by private companies, incentivized to maximize financial returns, may also support preliminary R&D, their level of funding is sufficient to finance late-stage clinical testing and commercial production.

### **Genetic Therapy**

A classification of medical approaches that involves manipulating the human genome. The term “genetic therapy” encompasses the following three technologies, which are distinct but not mutually exclusive: therapeutic genome editing, which involves permanent changes to the genome, either disabling, modulating, or restoring gene expression; traditional gene therapy, which relies on a viral vector to introduce a beneficial sequence of DNA; engineered cell therapy, which involves transplantation of autologous or allogeneic cells that have been engineered to introduce desired properties.

### **Good Laboratory Practice (GLP)**

A set of principles intended to safeguard the quality and integrity of non-clinical health and safety studies. GLP regulations set rigid standards for biotechnological research organizations, impacting how studies are carried out, planned, monitored, recorded, archived, and reported to ensure uniformity, consistency, reliability, and reproducibility of products in development.

### **Good Manufacturing Practice (GMP)**

Compliance of regulatory guidelines that set quality standards to ensure drug product safety and consistency. Rather than being product-specific like CMC, GMP is an overarching framework that applies to a manufacturer’s complete operation, including reagents, equipment, and personnel. Cell and gene therapy development encounters unique GMP challenges due to manufacturing complexity arising from biological variability of starting materials and complex supply chains and logistics.

### **Investigational New Drug (IND) application**

Request from a clinical study sponsor to the FDA, seeking authorization to administer an investigational drug or biological product to humans. Commercial INDs are usually filed by companies to obtain marketing approval for a new drug, while research or investor INDs are filed by a physician who both initiates and conducts a study on an unapproved drug or to study the repurposing of a drug for a new indication or in a new patient population. An IND application may include details on preclinical testing, manufacturing, investigator information, clinical trial protocols, and informed consent.

### **Licensing Agreement**

An agreement between the owner of intellectual property (IP) rights (licensor) and someone who is authorized to use the rights (licensee) in exchange for royalty fees. An exclusive license gives a licensee exclusive rights to IP, preventing the owner or any other third parties from using the IP. A non-exclusive license gives the IP owner the right to use the IP and licenses the IP to other third parties. Licensing agreements take into consideration territory, time period, and rights to future developments.

### **Low- and Middle-Income Countries (LMICs)**

A categorization of countries by the World Bank based on their gross national income (GNI) per capita. Low-income economies have a GNI below \$1,036; lower middle-income economies between \$1,036 and \$4,045; and upper middle-income economies between \$4,046 and \$12,535. While sometimes used interchangeably with the phrases “developing countries” and “global south”, LMIC only refers to the economies of countries. Of the world’s population, 74% live in middle-income countries and 10% live in low-income countries.

### **Modes of Therapeutic Delivery**

How to best deliver genetic cargo to target cells and tissues is an area of active research. Broadly speaking, a therapy can be delivered in vivo, ex vivo, or in situ. In vivo delivery refers to the administration of a genetic therapy directly into the patient’s body, such as infusion of a virus with target tissue specificity. In ex vivo delivery, patient cells (e.g. blood stem cells, immune cells) are first removed, modified to the desired function externally, and then re-infused into the patient. In situ delivery refers to the delivery or application of the genetic therapy directly on the target tissue. An example of in situ delivery is the recently approved therapy for Epidermolysis bullosa, Vyjuvek, which is directly applied to the patient’s skin.

### **Orphan Drug Designation**

Granted by the FDA, following a sponsor request, to a drug or biological product to prevent, diagnose, or treat a rare disease or condition. This designation incentivizes drug development by granting sponsors tax credits for qualified clinical trials, exemption from user fees, and a potential seven years of market exclusivity after approval.

### **Patients and Advocates**

Individuals living with conditions that could be treated using genetic therapy and chose to participate in the treatment journey, either for a clinical trial or approved therapy. The journey involves initial screening, enrollment, treatment administration, monitoring, and long-term care. Individuals such as caregivers and auxiliary groups (e.g., patient advocates, community organizations) play critical roles in supporting patients to ensure their physical, emotional, and financial wellbeing.



### **Payers (public and private)**

Organizations that bear the responsibility for making payment for a healthcare insurance or medical claim, and may include health plans, employers, health maintenance organizations, public entities such as government organizations (Medicare or Medicaid), among others.

### **Pharmacy Benefit Managers (PBMs)**

Third-party companies that act as intermediaries between insurance providers and pharmaceutical companies. Specialty-focused pharmaceutical management companies (SPBMs) are enabling the use of alternative financing models to mitigate risks associated with high-cost gene therapies.

### **Priority Review Voucher (PRV)**

Awarded by the FDA to drug sponsors upon approval of drugs treating neglected tropical diseases, rare pediatric diseases, and medical countermeasures. The voucher can be sold to another sponsor and used for a future drug application of the owner's choice. The FDA aims to complete priority reviews within six months compared to the standard 10-month review period.

### **Public Benefit Corporation (PBC)**

A type of for-profit corporate entity must produce a general public benefit, be transparent, and meet additional accountability criteria. Like C corporations, PBCs pay the same rate of corporate taxes and must report successes and failures to their shareholders annually. Importantly, PBCs have the ability to make decisions based on explicit non-financial goals and their obligation to shareholders without facing the risk of legal action.

### **Rare Disease**

The Orphan Drug Act defines a rare disease as one that affects less than 200,000 individuals in the US. Over 7,000 rare diseases affect more than 30M people in the US. The term 'ultra-rare' does not have a well-established threshold to distinguish it from rare disease categorization and has been used in a more context-dependent manner to indicate a sufficiently small patient population that renders drug development commercially challenging.

### **Real World Evidence (RWE)**

Clinical evidence regarding the use, potential benefits, and/or risks of a medical product. RWE uses real world data (RWD) which is any data collected during routine care delivery, including electronic health records, claims and billing activities, patient-generated data, and public health data. RWE is used to evaluate the long-term safety and efficacy of gene therapies in addition to assessing value for payment and reimbursement agreements.

### **Sponsor**

An individual, company, institution, organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. A sponsor may transfer duties to a contract research organization (CRO), but trial quality and integrity still resides with the sponsor.

### **Technology Transfer Office (TTO)**

Manages a university's intellectual property assets and the interactions or contractual relations with the private sector. TTO's may either receive interest from industry partners to bring academic-derived technologies to market or may seek industry partners for commercialization and market access purposes.

# 9. APPENDICES

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# 9. APPENDICES

## APPENDIX III: ADDITIONAL DISCLOSURES

Julia Barnes-Weise is a consultant to the Coalition for Epidemic Preparedness Innovation (CEPI).

Jonathan Esensten receives sponsored research funding from Multiply Labs, Inc. and Lonza, Inc. for the development of cellular therapy manufacturing devices. His research group received funding from Arsenal Bio. He serves on the scientific advisory board of Shennon Biotechnologies and holds equity in the company. He is named as an inventor on patent application for CRISPR-based gene editing (WO2021183850A1).

Paul Fehlner is Chief Legal Officer at Axcella Therapeutics and Acting Chief Legal Officer at Håber Biologics.

Donald Kohn is an inventor for the UC Regents on a lentiviral vector for gene therapy of ADA-SCID. The UC Regents have licensed intellectual property on which he is an inventor to ImmunoVec on lentiviral vectors. He is a member of the Scientific Advisory Boards and/or ad hoc paid consultant to Allogene Therapeutics, Pluto Immunotherapeutics, ImmunoVec, MyoGene Bio, Cimeio Therapeutics, Innoskel, and Cargo Therapeutics.

Rimas Orentas is on the scientific advisory boards of Umoja Biopharma and Abound Bio.

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