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GENE THERAPY

The translational gap for gene therapies in low- and middle-income countries

Kevin W. Doxzen[1]*, Jennifer E. Adair[2,3], Yris Maria Fonseca Bazzo[4], Daima Bukini[5,6], Kenneth Cornetta[7], Varsha Dalal[8], Renato Luiz Guerino-Cunha[9,10], Suradej Hongeng[11], Geeta Jotwani[12], Cissy Kityo-Mutuluuza[13], Krishnamurti Lakshmanan[14], Johnny Mahlangu[15], Julie Makani[5,6,16], Vikram Mathews[17], Margareth C. Ozelo[18], Savita Rangarajan[19,20], Janine Scholefield[21,22], João Batista Silva Júnior[23,24], Joseph M. McCune[25]

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Gene therapies are designed to address the root cause of disease. As scientific understanding of disease prevention, diagnosis, and treatment improves in tandem with technological innovation, gene therapies have the potential to become safe and effective treatment options for a wide range of genetic and nongenetic diseases. However, as the medical scope of gene therapies expands, consideration must be given to those who will benefit and what proactive steps must be taken to widen development and access potential, particularly in regions carrying a high disease burden.

INTRODUCTION

Gene therapy aims to modify or manipulate gene expression or to alter the biological properties of living cells for therapeutic use, an innovative medical approach that currently sits at an inflection point (*1*, *2*). After the first gene therapies developed in the 1990s, research and development (R&D) remained stagnant until the mid-2010s when the convergence of next-generation technologies spurred by multisectoral funding accelerated research exponentially. As of April 2024, 32 gene therapies have been approved globally for clinical use (*3*). More than 2000 gene therapies are in various stages of development, including 1500 in preclinical development and <10 entering preregistration (filing for regulatory approval) (*3*). Here, we define gene therapy using the definition coined by the American Society of Gene & Cell Therapy (ASGCT). This definition encompasses therapies that introduce a genetic sequence into target cells either in vivo or ex vivo. This definition of gene therapy includes genetically modified T cells, such as chimeric antigen receptor (CAR) T cells or T cell receptor–engineered T cell therapies, and other engineered cells, including natural killer cells and macrophages, but does not include unmodified donor cells or organs. We selected this definition because the infrastructure required and barriers confronting ex vivo gene therapy are similar to those for in vivo gene therapy. This definition excludes RNA-based therapies using messenger RNA (mRNA), RNA interference, or antisense RNA.

More than half of gene therapies target cancer, with neurological, muscular, metabolic, respiratory, and immunological diseases and blood and clotting disorders also being targeted (*3*). The ability of gene therapies to alter a wide range of DNA sequences creates market growth opportunities. As a result, the size of the global gene therapy market is expected to grow at a compound annual growth rate of 30.1% from 2023 to 2028 (*4*). At this pace, the market is forecast to increase from $6.93 billion in 2023 to $25.84 billion by 2028.

Collection and ex vivo modification of cells is the most widely used delivery strategy, accounting for 58% of gene therapies in development (*3*). Considerable effort has focused on improving adeno-associated viral (AAV) vectors and lentiviral vectors for in vivo delivery of the therapeutic gene, along with engineering of new lipid-based nanoparticles and other nonviral delivery vehicles (*5*). Increased costs associated with manufacturing viral vectors are a key driver behind the high price of gene therapies. Prices range from more than $400,000 per dose for Yescarta (axicabtagene ciloleucel), a CAR T cell therapy for large B cell lymphoma, to more than $4 million per dose for Libmeldy (atidarsagene autotemcel), a gene therapy for children with metachromatic leukodystrophy, a rare genetic disease affecting the brain and nervous system (*6*, *7*). These prices also reflect accrued R&D expenses, the curative and long-term nature of the treatments, and small patient populations in the case of rare diseases. Costs related to therapeutic administration, logistics, and posttreatment monitoring can add up to an additional $1 million per treatment (*8*).

As more gene therapies receive regulatory approval, establishing sustainable business models and achieving market access across diverse

[1]Strategic Analysis Inc., Arlington, VA, USA. [2]Translational Science and Therapeutics Division, Fred Hutchinson Cancer Center, Seattle, WA, USA. [3]Departments of Medical Oncology and Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA. [4]Department of Pharmaceutical Sciences, Faculty of Health Sciences, University of Brasília, Brasília, DF, Brazil. [5]Sickle Cell Programme, Department of Haematology and Blood Transfusion, Muhimbili University of Health & Allied Sciences (MUHAS), Dar-es-Salaam, Tanzania. [6]SickleInAfrica Clinical Coordinating Center, Muhimbili University of Health & Allied Sciences (MUHAS), Dar-es-Salaam, Tanzania. [7]Indiana University School of Medicine, Indianapolis, IN, USA. [8]Department of Health Research, Ministry of Health and Family Welfare, Government of India, New Delhi, India. [9]Centro Paulista de Oncologia, Grupo Oncoclínicas, São Paulo, SP, Brazil. [10]Instituto Oncoclínicas, Rio de Janeiro, RJ, Brazil. [11]Division of Hematology and Oncology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. [12]Indian Council of Medical Research, New Delhi, India. [13]Joint Clinical Research Centre (JCRC), Kampala, Uganda. [14]Department of Pediatric Hematology and Oncology, Yale School of Medicine, New Haven, CT, USA. [15]Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa. [16]Centre for Haematology, Department of Immunology and Inflammation, Imperial College London, London, UK. [17]Department of Haematology, Christian Medical College (CMC), Vellore, India. [18]INCT Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, SP, Brazil. [19]Advanced Center for Oncology, Haematology & Rare Disorders (ACOHRD), K. J. Somaiya Medical College & Research Center, Somaiya Ayurvihar, Mumbai, Maharashtra, India. [20]Faculty of Medicine, University of Southampton, Southampton, UK. [21]Bioengineering and Integrated Genomics Group, Next Generation Health Cluster, Council for Scientific and Industrial Research, Pretoria, South Africa. [22]Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa. [23]Brazilian Health Regulatory Agency–ANVISA, Brasília, DF, Brazil. [24]Department of Pharmaceutical Sciences, Faculty of Health Sciences, University of Brasília, Brasília, DF, Brazil. [25]HIV Frontiers, Global Health Accelerator, Bill & Melinda Gates Foundation, Seattle, WA, USA.
*Corresponding author. Email: kdoxzen@sainc.com

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health systems becomes more challenging. For example, in 2021, the gene therapy company bluebird bio closed operations in Europe after its inability to reach the requested reimbursement agreements for Zynteglo (betibeglogene autotemcel), a gene therapy for β-thalassemia priced at $1.8 million (*9*). Orchard Therapeutics, another company with approved gene therapies, discontinued investment for commercial reasons in programs for three rare primary immune deficiencies, including adenosine deaminase severe combined immunodeficiency, X-linked chronic granulomatous disease, and Wiskott-Aldrich syndrome, therapies that were spun out from a university hospital and a foundation (*10*). More recently, in November 2022, Hemgenix (etranacogene dezaparvovec), developed by uniQure and commercialized by CSL Behring, was approved by the US Food and Drug Administration (FDA) for gene therapy to treat hemophilia B, with an estimated price of $3.5 million, making it the most expensive medication in the world at the time (*7*). The financial incentives of being first-to-market can also disincentivize competing companies from continuing their research programs as demonstrated by recent corporate decisions surrounding gene therapies for sickle cell disease (SCD). In response to submissions to the FDA for regulatory authorization by CRISPR Therapeutics and Vertex Pharmaceuticals for Casgevy (exagamglogene autotemcel) and by bluebird bio for Lyfgenia (lovotibeglogene autotemcel), two gene therapies for SCD, other companies halted investments in their ex vivo SCD gene therapy clinical research (*11*). These business decisions and escalating prices highlight the complex interplay between public and private stakeholders across the entire gene therapy value chain.

Considering the challenges in market sustainability in high-income countries (HICs), the health and economic benefits of long-lasting or curative gene therapies are likely to be even more challenging globally. Gene therapy development and access to these technologies remain concentrated in HICs. More than 60 gene therapies in the United States are expected to receive approval by 2030, and estimates suggest that more than 1 million individuals in the United States will receive treatment by 2034 (*12*, *13*). However, this level of access to gene therapies will not be the reality for most of the world. In April 2024, of the 32 approved gene therapies worldwide, only 5 were granted regulatory approval in countries defined as low- or middle-income countries (LMICs) by the World Bank (*4*).

Clinical trials offer access to gene therapies in countries without approved products. In April 2024, there were approximately 1116 open gene therapy clinical trials (including those using CAR T cells) and RNA-based therapy clinical trials globally. Yet, none were open in low-income countries, and only 2.9% were recruiting trial participants in middle-income countries (not including China) (*14*). Even when LMICs can participate in international clinical trials, national populations may not benefit. One study revealed that, 5 years after approval by the FDA, 34 new drugs sponsored by large companies were approved for marketing in only 2 of 22 upper-middle-income countries and 2 of 9 LMICs, even when individuals in those countries participated in clinical testing (*15*). In addition, the global distribution of developers of therapeutics affects the location of clinical trials. In early 2023, of the 2760 worldwide developers of regenerative medicine therapies (including gene therapy, unmodified cell therapy, and tissue-engineered products), 1235 (44.7%) were in North America, 543 (19.7%) were in Europe, and 888 (32.2%) were in the Asia-Pacific region, most of which were in China (*16*). Only 94 (3.4%) developers were located in all other global regions, including South America and Africa.

Notwithstanding the overwhelming preponderance of gene therapy R&D in HICs, 90% of the global disease burden is shouldered by LMICs (*17*). To develop gene therapies that are safe and effective for all populations, clinical trials must be performed in these countries too. Given that biological and genetic diversity varies widely across populations, LMICs cannot rely solely on gene therapies developed and tested in HICs. For example, despite containing more genetic diversity than any other continent, only 2.5% of clinical trials are performed in Africa (*18*). Improving representation will involve supporting locally led clinical trials and attracting international pharmaceutical companies to partner with LMICs. This has historically been difficult because of long clinical trial application processes, lack of regulatory experience and political buy-in, and low profitability potential (*19*).

Country-specific agendas will facilitate closing the global gap by strategically guiding the sustainable development and delivery of gene therapies fit for national health systems and targeting diseases of national or regional importance (*20*). Here, we present six case studies focused on select LMICs with prevalent disease burdens (Fig. 1) that are potentially treatable with gene therapies currently under clinical development or approved in HICs, primarily the United States and European Union, or in research or approval phases in specific LMICs. We underscore the limited practicality and efficiency of developing translational pathways for these gene therapies using infrastructure and commercial models designed for HICs. The complex regulatory frameworks, trained workforce, sophisticated manufacturing, coordinated logistics, and advanced healthcare facilities required for gene therapies necessitate tailored capacity building constructed around the specific gaps and barriers in each country.

Building gene therapy capacity in LMICs will provide value for countless individuals worldwide. The types of innovations necessary to implement gene therapies in LMICs, including diagnostics, manufacturing, and therapeutic delivery, will ideally lower costs and increase competition, creating positive spillover effects for health systems globally.

ECONOMIC, INFRASTRUCTURE, AND POLITICAL CHALLENGES FOR SIX LMIC CASE STUDIES

To illustrate the range of possible global approaches for building gene therapy capacity, we present six LMICs, all actively engaged in gene therapy or related research, as case studies: Brazil, India, South Africa, Tanzania, Thailand, and Uganda (Fig. 1). Within these case study localities are a range of infectious and genetic disease targets that impose substantial public health burdens on the host country: hematological malignancies, hemophilia, hemoglobinopathies, and human immunodeficiency virus (HIV) infection (Fig. 1). The following country overviews examine specific preclinical or clinical gene therapy or related research activities targeting these high-priority diseases and describe select gene therapy clinical activities. The six case studies were also chosen because they cover a spectrum of parameters affecting gene therapy capacity, categorized as economic, infrastructural, and political.

Economic parameters include a country's allocation of domestic funds toward gene therapy R&D, the ability of citizens to access treatment through publicly funded health coverage, and the level of domestic funding dedicated to infrastructure. In addition, we consider the economic involvement of industry and the role of global, nongovernment organization (NGO) funders. Infrastructural parameters include workforce training (e.g., degree programs), existing clinical capabilities,

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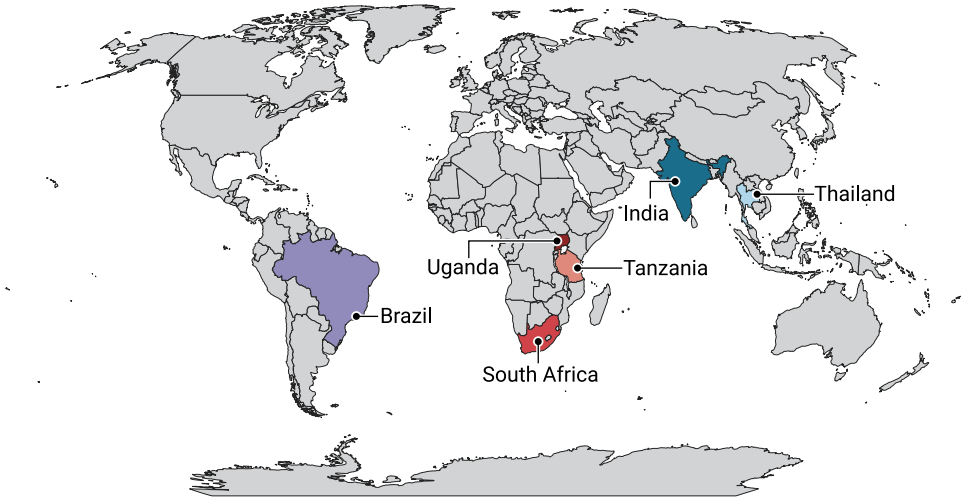

Brazil
Population 215.3 million

Hemophilia: 13,618 people living with hemophilia

Number of new cases per year:
Leukemia: 11,859
Non-Hodgkin's lymphoma: 11,093
Multiple myeloma: 5757
Hodgkin lymphoma: 2667

India
Population 1.4 billion

Number of new cases per year:
Leukemia: 49,883
Non-Hodgkin's lymphoma: 39,736
Multiple myeloma: 16,526
Hodgkin lymphoma: 9611

Thailand
Population 71.7 million

β-Thalassemia: 6480 infants born each year with severe β-thalassemia

Uganda
Population 47.3 million

HIV: 1.4 million adults ≥15 years old living with HIV

South Africa
Population 59.9 million

Hemophilia: 2404 people living with hemophilia

Tanzania
Population 65.5 million

SCD: 11,000 infants born each year with SCD

Fig. 1. Disease burden in six case study countries. Several gene therapies that are currently in development or have recently received approval target diseases that impose large health burdens on LMICs. Shown is the prevalence of high burden diseases in the six case study countries discussed in this Review: Brazil, India, Thailand, Uganda, South Africa, and Tanzania. For Brazil and India, the number of new cases annually is shown for leukemia, Hodgkin's and non-Hodgkin's lymphoma, and multiple myeloma. CAR T cell therapies are approved or being clinically tested for treating these diseases (*40*, *109*). For Brazil and South Africa, the total number of people living with hemophilia in each country is shown. Gene therapies using an AAV vector for in vivo targeting of liver cells for clotting factor production are approved or being clinically tested; other in vivo gene delivery approaches are under development (*25*). For Uganda, the number of adults aged ≥15 years living with HIV is shown, with HSCT currently under investigation as a durable treatment (*110*). For Tanzania, the number of infants born each year with SCD is shown, with HSCT currently being used as a durable treatment (*111*). For Thailand, the number of infants born each year with β-thalassemia major (the most severe form) based on gene frequencies is shown. An ex vivo gene therapy in which autologous hematopoietic stem cells are transduced with a lentiviral vector encoding a modified *HBB* gene is being tested as a durable treatment (*112*). Map designed using mapchart.net.

hospital infrastructure, and therapeutic delivery (e.g., building advanced manufacturing facilities). Last, political factors include whether regenerative medicine (a proxy and, in some cases, a precursor for gene therapy) is a national research priority and whether specific national policies and regulatory bodies exist at least regionally if not in the country itself (*21*).

HEMATOLOGICAL MALIGNANCIES AND HEMOPHILIA IN BRAZIL

Brazil, the home of more than 200 million people, is the seventh most populous country in the world. The life expectancy of Brazilians is steadily rising, and the proportion of its population age 65 or older is projected to triple by 2050, establishing it as the world's fourth-largest older population, behind only China, India, and the United States (*22*). As the population ages, it is predictable that there will also be a higher prevalence of cancer, including hematological malignancies such as leukemia, lymphoma, and multiple myeloma (Fig. 1).

Although the treatment outcomes for hematological malignancies have markedly improved in many countries because of the emergence of proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, these cancers remain largely incurable and are at risk for relapse (*23*). CAR T cell therapy, a form of gene therapy that combines antigen recognition and T cell signaling domains to program the immune system to eliminate carcinogenic cells, has been clinically proven to prolong survival and remission, leading to the approval of six different CAR T cell products by the FDA (*24*).

In Brazil, the Brazilian Health Regulatory Agency (ANVISA) is the country's regulatory authority tasked with approving drugs, advanced therapy medicinal products, medical devices, health services, and blood-, tissue-, and cell-based products. The first clinical trial using advanced therapy approved by ANVISA was for hemophilia in 2019. According to the World Federation of Hemophilia Global Survey, Brazil has the fourth-largest global population of people living with hemophilia in absolute numbers, with 13,618 individuals registered in 2022. Brazilians living with hemophilia have participated in gene therapy clinical trials since the first generation of trials was launched in the late 1990s (*25*). As of February 2024, 38 Brazilians with hemophilia have received gene therapy treatment at the University of Campinas (*26*). Currently, there are three phase 3 and one phase 1/2 clinical trials of gene therapy for hemophilia, approved by ANVISA, that are ongoing in Brazil (*27*). Recently, ANVISA approved the first commercial gene therapy product for adults with severe hemophilia A, Roctavian (valoctocogene roxaparvovec), made by the company BioMarin Pharmaceutical (*28*).

Clinical trials of gene therapies for hemophilia were, and continue to be, catalysts for developing regulatory frameworks within Brazil. Specifically, in December 2018, ANVISA passed resolution 260/218, establishing rules for conducting clinical trials with advanced investigational therapies, including gene therapies. Then, in April 2020, ANVISA resolutions 338/2020 and 363/2020 established the registration rules required for advanced therapy products.

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In 2022, ANVISA approved Brazil's first commercial CAR T cell therapies: Kymriah (tisangenlecleucel) for children and young adults with relapsed/refractory B cell acute lymphoblastic leukemia (ALL) and adults with relapsed/refractory diffuse large B cell lymphoma; Carvykti (ciltacabtegene autoleucel) for those with relapsed/refractory multiple myeloma; and Yescarta (axicabtagene ciloleucel) for diffuse large B cell lymphoma, primary mediastinal large B cell lymphoma, and follicular lymphoma (*29*–*32*). These three gene therapies were developed by pharmaceutical companies Novartis Pharmaceuticals, Janssen Pharmaceuticals, and Kite Pharma (a Gilead Company), respectively.

In Brazil, regulatory approval does not guarantee access to all individuals because the federal government is not required to add new therapies to the list of medications available through the country's national public health system, known as the Sistema Único de Saúde (SUS) (Unified Health System). Instead, the Ministry of Health, through a commission of specialists (CONITEC, or the National Commission for the Incorporation of Technologies), evaluates the costs and benefits of new treatments and makes recommendations for SUS. The role of CONITEC is similar to that of ICER (Institute for Clinical and Economic Review), an independent nonprofit organization, in the United States and NICE (National Institute for Health and Care Excellence), an executive nondepartmental public body sponsored by the Department of Health and Social Care, in the United Kingdom. Although currently approved CAR T cell therapies in the United States cost ~$400,000, their use can generate a per-patient total cost of between $700,000 and $1 million because of the management of treatment-related adverse events and subsequent procedures (*8*). Such costs would pose substantial challenges for roughly 75% of Brazilian citizens who rely solely on SUS, motivating the need for in-country development and manufacture of therapies with lower associated costs (*33*). Recently, the Brazilian Ministry of Health incorporated into the SUS the in vivo gene therapy Zolgensma (onasemnogen abeparvoveque) for treating spinal muscular atrophy type 1, priced in Brazil at a maximum value of 7 million reals ($1.33 million). A managed access agreement was signed, with payment in installments over 5 years that are linked to the long-term monitoring of the therapy's efficacy (*34*).

In August 2022, ANVISA approved the first clinical trial for the national development of a product based on CAR T cells for treating those with lymphomas and leukemias. The sponsor of the phase 1/2 clinical trial is the Hospital Israelita Albert Einstein, a private research center with public funding from SUS (*35*). In September 2023, another CAR T cell clinical trial, led by Brazilian researchers from the Fundação Hemocentro de Ribeirão Preto in partnership with the Butantan Institute, was approved by ANVISA. The early-stage clinical study (phase 1/2) aims to evaluate the safety and efficacy of treating those with relapsed and refractory B cell ALL and B cell non-Hodgkin's lymphoma (i.e., in cases of disease recurrence or resistance to standard treatment). The approval of this clinical trial is part of an effort by ANVISA to promote regulatory collaboration between the regulatory agency and Brazilian researchers and developers, aiming to boost and expedite the development of advanced therapy products available to SUS (*36*).

Several initiatives in Brazil have been launched to build a positive ecosystem for innovation and implementation of advanced therapy products. First, ANVISA has compiled and published several guides establishing a complete regulatory framework for Brazil, from preclinical development through product registration for commercial purposes (*37*, *38*). Second, the Brazilian federal government launched the Genomas Brazil Project (National Program of Genomics and Precision Health), which seeks to promote scientific and technological development in genomics and precision health within the scope of SUS, as well as to support the development of the national genomics industry. In practice, the new program will help to advance medical prevention, treatment, and diagnosis; finance research; provide technological advancements in advanced therapy medicinal products; and train new scientists in genetic disorders (*39*). Third, other agencies that support research in Brazil, such as the São Paulo Research Foundation (FAPESP), have launched initiatives trying to connect academic research groups and pharmaceutical companies. Whereas these efforts promote a positive environment for the discovery and translation of advanced therapies, Brazil will remain dependent on external technologies for the foreseeable future.

HEMATOLOGICAL MALIGNANCIES IN INDIA

In 2020, the estimated number of new cancer cases in India was 1,324,413 (*40*), a number that is likely to grow as the proportion of India's population aged 60 and above more than doubles (from 9% in 2015 to a projected 19% in 2050) (*41*). Like Brazil, the promising development of CAR T cell therapy as an effective treatment option for select cancers has attracted interest from Indian researchers, regulators, and patients.

In June 2020, the central government's National Biopharma Mission (NBM), Biotechnology Industry Research Assistance Council (BIRAC), and Indian Council of Medical Research, under the Ministry of Health & Family Welfare, approved funding equivalent to ~$3 million to conduct a first-in-human phase 1/2 CAR T cell clinical trial (*42*). The indigenous CAR T cell therapy technologies used in this trial arose from a collaboration between the Indian Institute of Technology (ITT)–Bombay and Tata Memorial Hospital (TMH), Mumbai in 2015. During the phase 1 trial, 6 children with ALL and 10 adults with B cell lymphoma were treated at the Advanced Centre for Treatment Research and Education in Cancer (ACTREC) of the Tata Memorial Center in Mumbai. In 2018, the group from IIT-Bombay spun off a company, ImmunoACT, and completed a phase 2 clinical trial. In October 2023, based on the data from that study, ImmunoACT received market authorization from the Central Drugs Standards Control Organisation (CDSCO), the country's pharmaceutical regulatory agency, becoming India's first CAR T cell therapy (*43*). The therapy will be accessible at 20 Indian government and private hospitals and is projected to cost 3 million to 3.5 million rupees (~$36,000 to $42,000) per patient. Apart from this trial, CDSCO has approved 10 other gene therapy clinical trials for diseases such as hemophilia, Duchenne muscular dystrophy, spinal muscular atrophy (as part of a global clinical trial), and others.

This R&D model of transitioning technologies from public laboratories to the private sector is also used in HICs, wherein preclinical development and early-phase clinical trials are conducted by academic centers, after which industry partners are identified or the technology is spun out into a new company to take the lead on more advanced clinical trial development. This strategy requires a strong investment presence, typically incentivized by an intellectual property protection infrastructure. In India, the lower cost of labor also enables lower-cost therapeutics, which can then be sold internationally.

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The Indian biotech start-up Immuneel Therapeutics launched the first industry-sponsored CAR T cell therapy trial in India, enrolling participants at Narayana Hrudayalaya, Bengaluru. Through technology transfer, Immuneel received exclusive rights to develop, manufacture, and commercialize in India CAR T cell therapy technology developed by Hospital Clínic de Barcelona and Institut d'Investigacions Biomèdiques August Pi i Sunyer in Spain (*44*). By establishing its own integrated cell therapy development and manufacturing facility at the Mazumdar-Shaw Cancer Centre at Narayana Health City (Bengaluru), Immuneel seeks to decrease production costs. In addition, Dr. Reddy's Laboratories, an Indian multinational pharmaceutical company, secured exclusive rights to Shenzhen Pregene Biopharma's anti–B cell maturation antigen CAR T cell therapy in India for relapsed or refractory multiple myeloma and received CDSCO approval for a phase 1/2 clinical study (*45*).

India is one of the few LMICs using both centralized and decentralized point-of-care manufacturing for CAR T cell therapy. A team at Christian Medical College, Vellore demonstrated that a decentralized manufacturing process for anti–CD19–CAR T cells using a fully automated closed system (Miltenyi CliniMACS Prodigy) is feasible in an LMIC setting (*46*). Evaluation of production costs in an academic, nonprofit context in India provided a benchmark for LMIC pricing, which could greatly increase access to this therapy.

Although the development and manufacture of more affordable therapies in India will improve access internationally, it remains to be seen how this will benefit the citizens of India. Roughly 70% of India's citizens do not have health insurance, paying out-of-pocket costs for healthcare. Its 28 states manage a mix of public and private healthcare facilities, with notable differences in cost and very large disparities in quality of care, not only between public and private facilities but also between urban and rural public facilities. Government initiatives like the National Policy for Rare Diseases 2021, which promises funding of 5 million rupees (~$60,000) per patient living with a rare disease, signify a step in the right direction for government support of unmet medical needs (*47*).

HEMOPHILIA IN SOUTH AFRICA

Although the prevalence of hemophilia, a rare genetic blood disease, is evenly distributed worldwide, management and treatment of the disease vary widely from one geography to the next. Hemophilia reduces a person's quality of life by 64% in upper-middle-income countries, by 77% in middle-income countries, and by up to 93% in low-income countries (*48*). Globally, an estimated 17.1/100,000 males are born with hemophilia A and 3.8/100,000 males are born with hemophilia B (*49*).

Hemophilia A and B are monogenic diseases, arising from mutations within genes encoding Factor VIII and Factor IX proteins, respectively, making these conditions attractive candidates for gene therapy. Beginning in the 1990s, gene therapy trials for hemophilia have enrolled individuals from around the world, with studies today involving participants from Japan, China, and India and future studies aiming to include participants from Peru, Vietnam, Thailand, Nepal, and Sri Lanka (*26*). South Africa is actively involved in multiple international gene therapy clinical trials for hemophilia, using facilities at the University of the Witwatersrand for therapeutic administration (*50*). Similar to gene therapy clinical trial participation in Brazil, involvement in international research enables access to gene therapies for those living with hemophilia in South Africa, in parallel with the development of domestic R&D and regulatory infrastructure.

South Africa's globally aligned regulatory and research ethics framework makes participation in international clinical trials possible. For gene therapy clinical research, approval is granted by the South African Health Products Regulatory Authority (SAHPRA) (*51*). In addition, the Department of Agriculture, Forestry and Fisheries regulates the import and export of genetically modified organisms for research purposes and oversees the registration of facilities. The country does not currently have regulatory frameworks for gene therapy manufacturing. Still, its regulatory infrastructure for vaccine manufacturing is sufficient for the increased production of vaccines for COVID-19 and other viruses. Plans to repurpose COVID-19 vaccine manufacturing infrastructure for gene therapy use are under discussion. Strategies for addressing gaps and barriers across health legislation, economics, and capacity building in South Africa have been proposed by researchers and may serve as a model for other LMICs (*52*).

SCD IN TANZANIA

SCD, a genetic blood disorder caused by the inheritance of two copies of a mutated hemoglobin subunit β (*HBB*) gene, is the leading genetic cause of mortality in children in Africa, accounting for 6 to 16% of deaths occurring under the age of five (*53*). In Tanzania, an estimated 11,000 babies are born annually with SCD, ranking the country fourth in Africa and fifth in the world for highest birth prevalence of SCD (*54*, *55*). In certain rural regions of Tanzania, the prevalence of SCD is as high as 3.9%, whereas the incidence for carriers, with one copy of the mutated gene, has an estimated prevalence of 31.6% (*56*). Given the relatively high prevalence of SCD and its health and economic costs (*57*), the Tanzanian Ministry of Health has designated SCD as a disease of national priority, seeking to increase survival rates by 50% through improved early detection (e.g., newborn screening) and providing comprehensive healthcare, including the intent to build capacity for advanced curative procedures (*58*).

In 2016, following a directive from the Ministry of Health, Tanzania began developing a strategy for cell and gene therapy, starting with establishing the Sickle Cell Program housed within the Muhimbili University of Health and Allied Sciences (MUHAS) (*59*). In 2021, hematopoietic stem cell transplants (HSCTs) were performed for the first time at Muhimbili National Hospital on the Mloganzila campus of MUHAS, using autologous stem cells to treat five individuals with multiple myeloma (*60*). This makes Tanzania the third country in sub-Saharan Africa (after South Africa and Nigeria) to conduct HSCT, providing it with infrastructure that should later facilitate the introduction of ex vivo gene therapies for SCD (*61*). By September 2023, four children had undergone HSCT for SCD at Benjamin Mkapa Hospital in Dodoma using human leukocyte antigen (HLA)–matched donors. In addition, the government of Tanzania has pledged 5 billion shillings ($2 million) to support specialized services, including HSCT for 20 individuals living with SCD.

Meanwhile, a collaboration between the Bill & Melinda Gates Foundation and the US National Institutes of Health seeks to incentivize research that will ultimately move the field from ex vivo to in vivo approaches, hopefully creating cures for SCD and HIV that are more accessible and affordable (*62*). A collaboration between MUHAS and the Novartis Institute for Biomedical Research (NIBR)

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to advance in vivo gene therapy for SCD in Africa has facilitated the development of a draft target product profile (TPP) for ex vivo and in vivo gene therapies for SCD. Similar collaborative efforts have led to a TPP for an HIV cure in Africa (*63*).

MUHAS intends to build a Sickle Cell Institute on the Mloganzila campus, which will include a Centre of Excellence for cell and gene therapy. In the interim period, MUHAS has allocated space to establish a cell and gene therapy laboratory within Mloganzila campus's Centre of Excellence for Cardiovascular Sciences. Clinical leaders and advocates in Tanzania have forged several partnerships to establish local and international collaborations vital in driving the country's gene therapy agenda. Partners such as Caring Cross (a US-based nonprofit that supports the development and affordable access of advanced medicines), German Bone Marrow Donor Center (DKMS), and the European Society for Blood and Marrow Transplantation (EBMT) have all visited Tanzania for initial assessments of the country's infrastructure capacity.

Although no gene therapies for SCD are approved or tested in Tanzania or in any other country in Africa, Tanzania has been actively engaged in preparing patients and personnel for clinical trials as well as focused on the conduct of supporting basic, clinical, and social science research (*64*).

β-THALASSEMIA IN THAILAND

β-Thalassemia is another inherited disease resulting from mutations in the hemoglobin β (*HBB*) gene. For this reason, gene therapy approaches restoring a functional copy of the *HBB* gene can provide clinical benefit in the setting of both SCD and β-thalassemia. Asia and the Middle East account for 95% of β-thalassemia births globally (*65*). Within Thailand, the prevalence of β-thalassemia, based statistically on phenotype, is 3 to 9% (*66*). Only 20% of people in Thailand living with β-thalassemia major, a severe form of the disease, live to 40 years of age, underscoring the potential benefits that might be provided by curative therapies (*67*).

Efforts to develop gene therapy products are underway in at least three major medical universities in Thailand, with varying degrees of collaboration with US and European partners and within Asia. An international gene therapy clinical trial funded by the US-based pharmaceutical company bluebird bio, involving researchers from Thailand's Ramathibodi Hospital, Mahidol University, recently concluded (*68*). This global study evaluated the safety and efficacy of betibeglogene autotemcel, an ex vivo gene therapy in which autologous hematopoietic stem cells were transduced with a lentiviral vector encoding a modified *HBB* gene. Betibeglogene autotemcel, sold under the brand name Zynteglo, received conditional marketing authorization by the European Medicines Agency (EMA) and regulatory approval from the FDA and is awaiting Thai government approval (*69*, *70*).

The Thai government has taken steps to offer coverage for high-cost procedures. Those undergoing HSCT and other stem cell therapies receive >$35,000 to assist with treatment costs, a price point that may be within reach for gene therapies manufactured locally (*71*). Currently, cells are shipped to Australia or Japan for gene transduction, contributing enormous costs to the production process and motivating investments from Thailand's public and private sectors toward local manufacturing. For example, researchers from Mahidol University are using a Good Manufacturing Practices (GMP) unit at the university's hospital to produce a locally developed lentiviral vector for ex vivo transduction of hematopoietic stem cells.

In the private sector, Genepeutic Bio, a gene therapy contract development and manufacturing organization, established the country's first GMP-certified manufacturing facility at the Thailand Science Park in Pathum Thani, an innovation hub designed to attract investments and spur private sector growth. Genepeutic Bio is the first company to submit an application to the Thai FDA to initiate a clinical trial using an advanced therapy medicinal product; the first CAR T cell product in their pipeline has entered a phase 1/2 clinical trial. With Thailand's Bio-Circular-Green Strategic Plan—which seeks to boost investment in capacity building in technology, human capital in R&D, and production technology for vaccines, biopharmaceuticals, and medical devices—the country is striving to become a leading hub of gene therapy innovation in Southeast Asia (*72*). To ensure that Thailand can effectively collaborate with international partners and enter new markets, the country's regulatory agencies continue to promote harmonization with the United States, European Union, Japan, Australia, and neighboring countries.

HIV IN UGANDA

At the end of 2020, an estimated 0.7% of adults aged 15 to 49 years were living with HIV worldwide, but in Uganda, the prevalence of HIV in the same age group was approximately 5.5% (*73*, *74*). Although antiretroviral therapy (ART), the current standard of care, has been proven to greatly increase life expectancy, its use alone will not stop the HIV epidemic. The Joint United Nations Program on HIV/AIDS proposed a target for epidemic control by 2030 that will require 95% of individuals living with HIV to know their status, 95% of whom will be on ART and will have sustained viral load suppression. This will equate to both better health outcomes and an inability to transmit the virus. Despite this goal, more than 1.5 million new HIV infections occur annually.

Many people living with HIV cannot access effective medications, whereas those with access to care must take daily pills for the rest of their lives. Sustained adherence to pill regimens has been inconsistent, contributing to 650,000 deaths a year from AIDS worldwide. An HIV "cure" would obviate the current requirement for long-term administration of ART either by controlling the virus in the absence of any ongoing treatment such as ART (remission) or by completely removing replication-competent virus from the body (eradication). A one-time treatment would eliminate the need for lifelong intervention, and efforts are now being advanced to determine whether gene therapy might serve to reach this goal.

The Joint Clinical Research Centre (JCRC) in Kampala, Uganda is procuring and installing the necessary equipment and is training specialized staff to perform the country's first HSCT for SCD in 2024. Meanwhile, the Uganda Cancer Institute is preparing to treat cancer using bone marrow transplantation. In addition, JCRC plans to establish requisite infrastructure for gene therapies and will be evaluating in vivo gene therapy treatments for hemophilia A with industry partners. Clinical researchers at JCRC are founding members of the Global Gene Therapy Initiative (GGTI), an international alliance of key stakeholders including clinicians, scientists, engineers, advocates, community members, individuals living with disease, and their caregivers, all working toward enabling access and implementation of gene therapies as curative medicines for high-prevalence, incurable diseases in LMICs (*75*). GGTI aims to facilitate capacity building in LMICs by matching local institutes with global funders and gene therapy companies to procure critical resources and to assist with

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international technology transfers. In Uganda, GGTI works with the JCRC to advance gene therapies for the treatment of HIV and SCD. Additional assistance is coming from the World Health Organization, which is providing guidance on regulatory reform, as well as from the government of Uganda, which has committed to supporting infrastructure development for gene therapy delivery in a phased manner over the next few years. The intent is for these efforts to serve as an exemplar for other LMICs.

THREE DIFFERENT SPHERES FOR GENE THERAPY CAPACITY

The successful development and delivery of gene therapy within any country is contingent upon functional capacity and effective coordination across three distinct spheres: academic, government, and commercial (Fig. 2). These domains are not entirely specific to gene therapy; rather, they apply to the preclinical research, human testing, regulatory approval, and market integration of any healthcare technology. Yet, the sophisticated equipment, highly trained personnel, and complex regulatory programs required to develop and deliver gene therapies necessitate a high degree of capacity building and unique capabilities across the academic, government, and commercial spheres. By understanding the function of each sphere as it relates to gene therapy, we can begin to identify opportunities to build partnerships and establish processes that advance transformative health technologies in low-resource settings (Fig. 2).

The academic sphere

The academic sphere serves as an incubator for people, ideas, and projects (Fig. 2). Specialized workers (including technicians, computational biologists, and social scientists) receive training within accredited higher-education institutions. The number of these specialized workers is actively growing across Latin America, East and South Asia, the Middle East, and North and Sub-Saharan Africa. The number of specialized workers has nearly doubled from approximately 40,000 to nearly 70,000 between 2006 and 2018, with a 91% increase in student numbers growing from 78.6 million to 150.2 million, approximately 69% of whom were in public institutions (*76*). Despite these trends, considerable heterogeneity (e.g., in terms of biological sex and gender) exists in educational attainment within and between countries (*77*).

A subset of academic institutions are connected to research hospitals (e.g., Uganda's JCRC and Thailand's Ramathibodi Hospital, Mahidol University), enabling the training of clinical specialists and the formation of multidisciplinary teams required to lead or participate in clinical trials. Academic centers play a crucial role in technology development that can be patented and licensed to start-up or established companies or that can be used by investigators for an in-house clinical trial.

Building manufacturing capacity and simplifying complex supply chains in research hospitals will be critical for clinical trial efficiency, as will be the institution and maintenance of GMP facilities. Although these efforts are expensive, it is only with such capacity in place that a transition can occur from preclinical research to clinical trials (*78*). The emergence of place-of-care manufacturing in hospital settings made possible by benchtop devices will further simplify processes and reduce the number of required personnel (*46*).

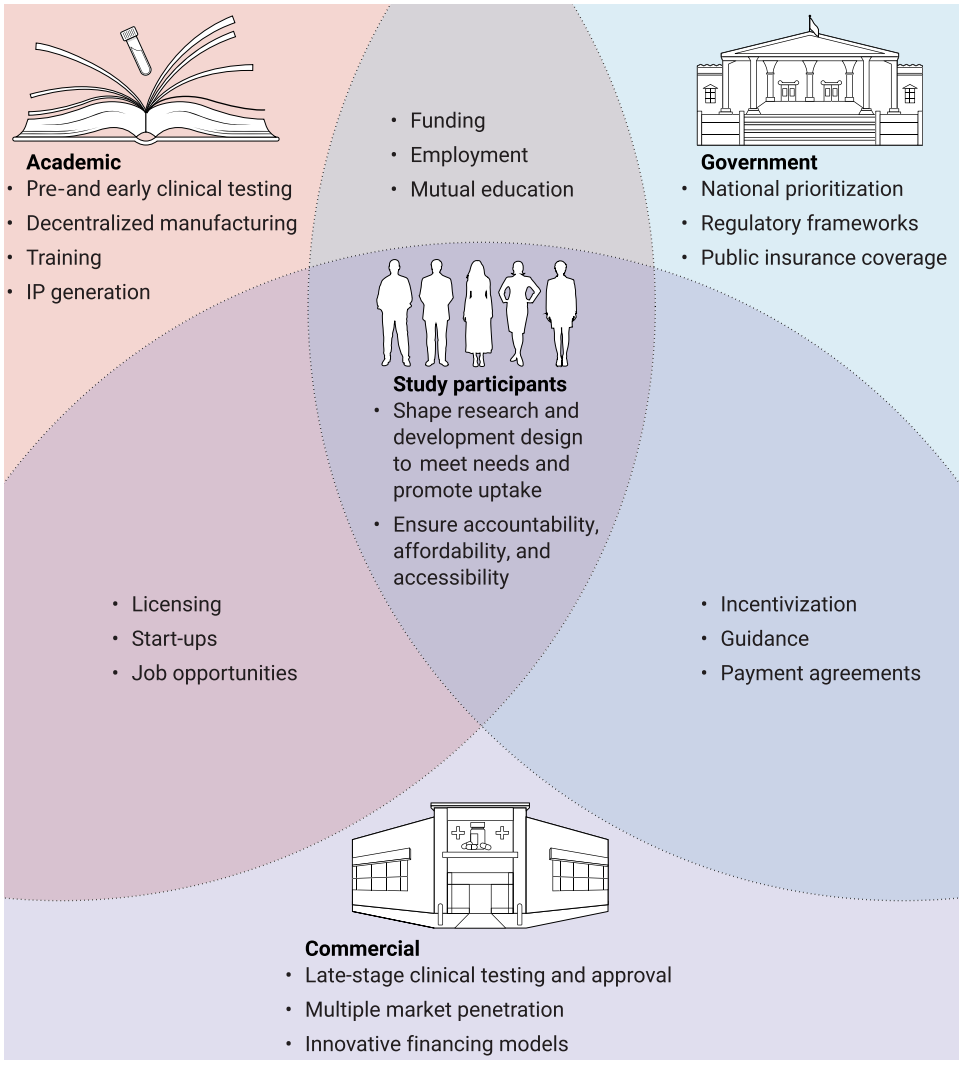

Fig. 2. Three different spheres for building gene therapy capacity. Shown is the intersection of academic, government, and commercial spheres and how they affect the development and delivery of gene therapies. The academic sphere trains the workforce, develops in-country technologies, generates intellectual property (IP), and conducts preclinical and early clinical testing. The government sphere sets national priorities and establishes regulatory frameworks. The commercial sphere helps to bring therapies to market and creates financing models to enable patient access while maintaining profits. Although each of these spheres has unique capabilities and responsibilities, close coordination among the spheres is needed to ensure the successful development and delivery of gene therapies in LMICs.

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The government sphere

The government sector acts as both an enabler and a gatekeeper. By declaring specific diseases as national priorities (e.g., SCD in Tanzania or rare diseases and hemoglobinopathies in India) or by incorporating gene therapy technology into national development plans (e.g., the Bio-Circular-Green Strategic Plan in Thailand), governments can rally attention and resources around the strategic development and deployment of gene therapies.

Through regulatory frameworks and guidance documents, governments dictate how research institutions participate in or initiate clinical trials. The unique nature of these treatments that manipulate gene expression or alter the biological properties of living cells makes them challenging to regulate within traditional frameworks. This tension is forcing regulators globally to either stretch the boundaries of their existing medicinal product regulations or design and implement new regulations (*79*). Most regulators in LMICs have chosen to repurpose existing policies and frameworks to accommodate gene therapy products, although countries such as Brazil have recently established specific frameworks that combine elements of different regulatory models (*80*).

After regulatory approval, governments oversee market access and coverage of the cost of gene therapies, sometimes using health technology assessments or other value estimate tools to determine cost-effectiveness (*81*). Experimentation and agile implementation, by governments and private insurers, with alternative payment and reimbursement models will be critical for improving access across all demographics. In February 2023, the US Department of Health and Human Services launched the Cell and Gene Therapy Access Model, a pilot study led by the Centers for Medicare & Medicaid Services (CMS) Innovation Center. This pilot study will involve coordination among state-based Medicaid agencies and CMS to facilitate multistate outcome-based agreements with manufacturers for certain cell and gene therapies. The initial focus will be cell and gene therapies for SCD (*82*).

The commercial sphere

In large part, because 86% of drugs that enter clinical trials do not receive FDA approval, it takes approximately $2.6 billion in aggregate to bring a single drug to market in the United States (*83*, *84*). Uncertainty regarding long-term durability and the lack of clarity about healthcare coverage add additional risk to the commercial viability of gene therapies. Despite this unpredictability, companies are investing heavily in new treatments and playing an important role in scaling production (e.g., establishing manufacturing facilities and training personnel for mRNA vaccine production), which countries intend to leverage for gene therapy purposes (*85*). Companies also have the expertise and resources to navigate different regulatory regimes and introduce gene therapies into different markets.

The high costs associated with gene therapy manufacturing and administration force companies to experiment with different corporate models such as voluntary licensing, donation programs, value-based tiered pricing, and subscription models to maintain profitability within and across different countries. Benefit corporations also play an important role in LMICs by incentivizing social responsibility, which can result in more widely accessible technology transfers and market-consistent pricing (*86*). Crowdfunding is emerging as a potential platform for financially supporting expensive therapies, yet such payment models raise several legislative and regulatory challenges (*87*).

INTERACTIONS OF ACADEMIC, GOVERNMENT, AND COMMERCIAL SPHERES

The academic, government, and commercial spheres are intimately linked, and the dynamic interplay between them might affect the rate of development and community reach of gene therapies. Governments contribute substantial funds to academic institutions and exert considerable influence over the direction of academic research as well as the translation of basic research into clinical testing. Government officials educate university researchers on regulatory processes; conversely, researchers work with these officials to update regulations that enable academic research and clinical trials. Governments also employ many doctors and researchers through universities and public hospitals, affecting both the supply and demand of a trained workforce. Without career opportunities, skilled workers in LMICs will likely migrate to HICs, resulting in a "brain drain."

Academia and industry often play collaborative roles in bringing a candidate therapeutic intervention from basic research through clinical validation to market access. Whereas universities excel in basic research, discovery, and phase 1 clinical studies, companies have the resources and expertise to conduct later-phase clinical trials and to scale products efficiently. A strong industry presence also plays an important role in the employment of workers trained at universities, further bolstering the economy (e.g., Thailand's Science Parks) (*88*).

Governments interact with the commercial sphere through the incentivization of the private sector. Building science parks and innovation hubs serves to centralize resources, incubate start-ups, and attract multinational companies. Informal regulatory meetings, such as the FDA's INTERACT meeting, provide opportunities for companies to engage regulators during the early stages of clinical trials. Operational barriers, including lengthy regulatory mechanisms, are a recurring challenge in LMICs because such barriers can delay recruitment of participants into clinical trials by several months and disincentivize industry engagement (*19*).

Study participants at the intersection of the three spheres

Those individuals who choose to become engaged in clinical trials sit at the intersection of the three spheres. Along with caregivers and advocates, such participants must be included throughout the R&D process in academia and industry to help shape research design and clinical validation as well as to ensure that a safe and effective cure meets the physical, mental, and emotional needs of the individual as well as the economic and social needs of their communities.

By informing the design and execution of research, access to healthcare, and the creation of policy, study participants, along with caregivers and advocates, can improve the acceptability of therapies, ensuring that emerging treatments address clinical problems ethically and effectively while also suiting an individual's lifestyle (e.g., from the standpoint of culture, beliefs, and daily activities). These individuals also hold government officials, industry leaders, and funders accountable to ensure that therapies are affordable and accessible across diverse socioeconomic and geographic groups.

SHARED AREAS OF CAPACITY BUILDING IN LMICS

There is no single strategy directing how lifesaving gene therapies might be developed and sustainably delivered on an equitable basis to low-resource settings. The political, economic, and infrastructure circumstances of a given country will uniquely influence how academic, government, and industry spheres must evolve and interact to make

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gene therapy a realistic treatment option. That said, common challenges will no doubt be faced by all countries, although pathways for capacity building and implementation may differ. Shared areas of capacity building within and across LMICs such as health facilities, R&D, workforce, manufacturing, community engagement, and finance must occur to maximize the long-term viability and impact of gene therapies.

Health facilities

The lack of equitable access to healthcare is a pervasive problem across nearly all countries, one that will be further exacerbated by the introduction of gene therapies that are currently very expensive and dependent on complex infrastructure housed in specialized facilities. The proposed "hub-and-spoke" model of coordinated care centralizes gene therapy administration in advanced tertiary care facilities ("hubs"), using primary and secondary care facilities ("spokes") as home centers where education, screening, and long-term follow-up occur (*89*).

In India, approximately 70% of the population lives in rural areas, while 95% of cancer care facilities (including tertiary care centers and specialist doctors) are in urban areas (*90*). Similarly, a 2019 study identified 299 specialty oncology services in health facilities across Brazil, all of which were concentrated in just 173 (3.1%) of the country's 5570 municipalities (*91*). Although specialty facilities cannot possibly exist everywhere, and hub-and-spoke models may help to streamline referrals, country-level distribution of treatment centers is a critical factor affecting access.

Research and development

Building domestic R&D infrastructure sufficient to conduct clinical trials in LMICs is necessary to capture the vast biological and social diversity across and within countries. Countries are likely to experience variability in the safety and efficacy of gene therapies across populations, and those gene therapies developed with one population in mind may not be transferrable to others. For example, South African participants in gene therapy clinical trials for hemophilia A and B showed a high prevalence of antibodies to specific AAV serotypes (*92*, *93*). Similarly, studies in India have identified high levels of preexisting antibodies to an AAV vector among >90% of adults with hemophilia B (*94*). In gene editing experiments, studies have revealed that genetic diversity can lead to unanticipated off-target effects (e.g., cutting at unintended genome sequences), reducing the treatment's therapeutic efficacy (*95*).

These safety findings highlight the need to develop gene therapy products that account for parameters such as variable prevalence of anti-vector antibodies and genetic heterogeneity, data that are unlikely to be collected unless R&D is performed in LMIC settings. One way of collecting safety data is through long-term monitoring of those engaged in gene therapy clinical trials. By following individuals for months or years after gene therapy administration, researchers can detect delayed adverse events and evaluate a therapy's sustained efficacy, which can be used to iteratively improve the treatment design and adjust payment agreements (e.g., outcome-based payments).

In the United States, the FDA suggests that long-term follow-up studies monitor gene therapy trial participants for 5 to 15 years, depending on the nature of the gene therapy (*96*). In LMICs, limitations in electronic health record infrastructure, distances to healthcare facilities, and other factors could introduce substantial hurdles for reliable, multiyear follow-up. The implementation of a hub-and-spoke model of care delivery could reduce travel distances for those who must be followed. Similarly, the use of mobile health technologies could also lessen travel burdens by tracking health outcomes remotely (*97*). International nonprofit organizations can play a pivotal role in organizing and funding data collection and analysis, particularly for long-term monitoring. For example, the World Federation of Hemophilia supports the Gene Therapy Registry, a prospective, observational, and longitudinal registry designed to collect long-term data on people with hemophilia who receive gene therapy (*98*). Such organizations also play key roles in supporting treatment and care, patient advocacy, and education and training.

Manufacturing

There is a global shortage of gene therapy manufacturing capacity, with hundreds of new facilities needed to meet the estimated demand for currently approved therapies (*99*). As HICs continue to build centralized manufacturing facilities, LMICs will need to develop sustainable and resilient manufacturing strategies that balance near-term needs that may require outsourcing to HICs with long-term goals of building domestic capacity and achieving self-reliance. Reaching a cost-effective price point will require point-of-care manufacturing. Researchers at the Christian Medical College in Vellore, India demonstrated the feasibility of this approach by producing CAR T cells in house (*46*). When considering the optimal manufacturing approach for a given setting and disease target, countries must also consider licensing costs. They may consider licensing from academic institutions or companies in HICs at an affordable price (e.g., the Caring Cross model) or develop technologies locally through domestic R&D (*100*).

Workforce

Whereas large youth populations in LMICs present an opportunity to train and grow the requisite workforce for developing and delivering gene therapies, the global health workforce is projected to operate at a deficit for the foreseeable future, with the largest shortages in African and Eastern Mediterranean regions (*101*). The World Health Organization recommends one clinical hematologist per 100,000 people in every country, yet South Africa has fewer than one per 2 million, while many other countries in sub-Saharan Africa have even fewer (*102*). The introduction of gene therapies could overstretch the demand on clinical specialists, yet many public and private hospitals in LMICs do not have the resources to hire additional highly trained staff. The government and academic spheres must work together to maintain the delicate supply and demand of trained health workers necessary to support a growing gene therapy screening, administration, and monitoring ecosystem.

International collaboration among academic institutions is a critical component in training the next generation of gene therapy scientists across LMICs. In 2022, the Global Outreach Committee of the American Society of Gene & Cell Therapy ran their first iteration of the Global Gene Therapy Training course (formerly called "Training the Trainers") in partnership with MUHAS in Tanzania (*103*). The course equipped 45 full-time academic faculty with the information and resources to integrate gene therapy education into their own curricula.

Community engagement

Patients, caregivers, and advocates play essential roles in voicing the concerns and interests of communities during the design and execution of clinical trials. This often takes the form of community advisory boards (CABs). CABs also help to create culturally attuned and up-to-date educational materials for their respective communities. One organization working to educate and empower community members is the Joint Adherent Brothers and Sisters Against AIDS

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(JABASA) community-based organization in Uganda. JABASA informs the general community about the importance of emerging research like gene therapy, particularly for HIV and SCD, helping to bridge the gap between those developing these treatments and those who may receive them. Another such advocacy group is the National Alliance of Sickle Cell Organisations (NASCO) in India, composed of more than 17 NGOs and health sector organizations. NASCO seeks to elevate the voices of persons living with SCD, including advocating for access to diagnostic testing, effective treatments, and potential curative therapies, including gene therapies. Religious leaders and organizations can also serve as bridges between researchers and community members, helping to navigate spiritual, ethical, and social questions and concerns surrounding alterations of the human genome.

Finance

Economic projections suggest that private sector innovation will reduce the costs of an in vivo gene therapy cure for HIV to between $10,000 and $50,000 per dose in HICs over the next 10 years (20). In contrast, an HIV cure would need to cost and be priced at $1000 to $2000 in LMICs to be cost effective relative to ART (*104*). This suggests that support from outside of the private sector is necessary to fund technological innovation and pay for approved products. The collaboration between the Bill & Melinda Gates Foundation and the US National Institutes of Health to develop single-shot genetic cures for HIV and SCD is an example of philanthropic and HIC government funding that supports high-risk research, which may not align with private sector incentives (*105*).

Once an approved gene therapy is available, LMIC governments will need to consider whether and how these costly procedures are incorporated into public insurance plans, particularly as LMICs pursue universal health coverage goals. Part of this decision will depend on negotiated financing models enabled through public-private partnerships. These may include voluntary licensing, donation programs, value-based tiered pricing, and subscription models (*81*). For some diseases, long-standing funding opportunities may already exist. For example, the President's Emergency Plan for AIDS Relief (PEPFAR) in the United States has invested more than $100 billion in the global HIV/AIDS response since its inception in 2003. If national health agencies approve a gene therapy cure for HIV and the price is deemed cost effective compared with other treatment alternatives, then PEPFAR may allocate funding to this advanced treatment option (*106*).

The decision to fund gene therapies sits within the broader issue of resource allocation to maximize population benefits. The cost of gene therapy for one individual could provide lifesaving treatment for hundreds or thousands of individuals with imminently treatable conditions, such as common infections, malnutrition, and dehydration. Country leaders must perform objective-setting exercises to assess priorities (e.g., political and economic) and determine whether investments in gene therapy programs will achieve sufficient benefits to targeted or general populations, considering both practical and ethical factors (20). As demonstrated by the six case studies discussed here, focusing on specific disease areas helps to narrow resource allocation conversations, forming a focal point around which partnerships can form and infrastructure can be tested, before expanding to other diseases (*107*).

Policy and regulation

Governments across LMICs should not adapt existing regulations or establish new frameworks in isolation but instead should consider regional harmonization to promote collaboration and knowledge sharing, which can help to reduce dependence on HICs. For example, all African countries have some type of established administrative national medicines regulatory authority, with varying capacity for market authorization, pharmacovigilance, post-market surveillance, quality control, and clinical trials oversight. The recently formed Africa Medicines Agency offers an opportunity to enable regional regulatory harmonization and convergence, with a vision toward continental level harmonization (*108*). Regulatory alignment across borders will be critical for testing and scaling local manufacturing of gene therapy products, which currently present capacity challenges for individual national medicines regulatory agencies.

CONCLUSION

Understanding the value that a long-lasting treatment, such as one offered by gene therapy, can provide to individuals affected by various diseases and society is vital for countries in determining if, how, and when such therapies may compete with existing priorities and fit within national agendas. The six case studies outlined here examine diverse governments, research institutions, and companies that are striving to be early gene therapy adopters. The success of these stakeholders and the inclusion of LMICs into a growing global market will hopefully improve patient access worldwide and pave the way for equitable distribution of lifesaving gene therapies not only in LMICs but also in resource-limited regions that exist in HICs. Finding ways to manufacture and administer gene therapies in resource-constrained settings will hopefully lead to more affordable, accessible, and acceptable technologies and processes, ultimately paving the way for their benefits to be appreciated on a global basis.

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