

In collaboration with Thunderbird School of
Global Management and Sandra Day O'Connor
College of Law at Arizona State University



Accelerating Global Access to Gene Therapies: Case Studies from Low- and Middle-Income Countries

WHITE PAPER
OCTOBER 2022



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Foreword

Gene therapies could widen the global health gap, but proactive capacity building in LMICs can enable access to these life-altering treatments.



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Gene therapy is at an inflection point, spurred by advances in genome engineering and other biotechnologies. Thousands of these therapies are in development, a number that is exponentially rising and likely to lead to dozens of approved treatments entering health systems over the next decade. Designed to address the underlying cause of a disease at a genetic level, this emerging form of medicine has the potential to offer new cures. Such therapies are often single-administration, which is a holy grail of medical interventions.

However, too often the benefits of advanced healthcare technologies remain restricted to high-income countries, a reality that is anticipated may befall gene therapies. The sophisticated equipment, complex regulatory systems and expert personnel required to develop and deliver gene therapies, together with funding issues, pose significant challenges for low- and middle-income countries (LMICs).

With appropriate foresight, proactive capacity building and financing mechanisms, LMICs can not only offer these revolutionary therapies to communities with high burdens of disease, but meaningfully shape the global market. The COVID-19 pandemic revealed the consequences of ignoring LMICs in the development and dissemination of

healthcare technologies. Gene therapies present an opportunity to learn from these experiences and help close the global health equity gap.

This joint publication by the World Economic Forum, Thunderbird School of Global Management and Sandra Day O'Connor College of Law at Arizona State University aims to shed light on the complex field of gene therapy. The report provides a broad overview of the interconnected areas of infrastructure required to sustainably build gene therapy capacity in low-resource settings.

Co-authoring this report with clinical leaders in LMICs who are actively engaged in gene therapy research offered an opportunity to hear and compare the struggles and successes of early adopters. This report seeks to elevate the voices of local champions working to bring gene therapies into their own clinics.

We hope this publication will both motivate and guide action by policy-makers, health-systems leaders, pharmaceutical companies, funders and other stakeholders. Gene therapy provides a realistic opportunity to advance the economic, health and political agendas of LMICs. Assembling country roadmaps for gene therapies now will ensure these medical interventions benefit patients globally.

Executive summary

Gene therapy is at the forefront of modern medicine. By making precise changes to the human genome, these sophisticated technologies can potentially lead to one-time lifelong cures. As of mid-2022, more than 2,000 gene therapies were in development worldwide, contributing to a global market value that is expected to reach nearly \$20 billion by 2027.^{1,2} Researchers are applying gene therapies to infectious and non-communicable diseases (e.g. HIV, sickle cell disease) that affect tens of millions of people around the globe, most of whom live in low- and middle-income countries (LMICs).

Although these disease burdens disproportionately fall on LMICs, the majority of gene therapy research and development (R&D) and clinical testing has remained restricted to high-income countries (HICs), primarily the United States and in the European Union (and increasingly China). The complex equipment, expert personnel and mature regulatory environments necessary to develop, test and administer gene therapies are largely insufficient or absent in LMICs. Without concerted efforts to build gene therapy capacity in low-resource settings, the global health divide is likely to widen.

To understand the unique barriers hindering LMICs from entering the global gene therapy market, this report examined five LMICs (Uganda, Tanzania, South Africa, Thailand and India) that are actively pursuing gene therapies, targeting a broad spectrum of diseases (HIV, HBV, sickle cell disease, beta thalassaemia, haemophilia and select cancers).

Seven areas of capacity building were identified as essential pillars for sustainably supporting the long-term development and delivery of therapies in LMICs.

Capacity pillars

- **Research and development (R&D)** ecosystems connecting health and social science areas aligned with national and institutional strategic plans
- **Health facilities** equipped with sophisticated equipment and strategically located to serve patients
- **Manufacturing** localized to treatment-delivery sites to lower costs and increase speed
- **Workforce** trained in diverse disciplines and retained across public and private sectors
- **Community engagement** from the beginning of R&D to improve accessibility, affordability and acceptability

- **Policy and regulation** converged across HICs and LMICs, promoting work-sharing and reliance, and accelerating clinical trials and commercialization
- **Finance** using public-private partnerships to ensure all patients have access to effective cures

Case study countries were chosen to represent different levels of gene therapy readiness. Those with less capacity (i.e. Uganda and Tanzania) directed their resources towards equipping health facilities and establishing regulatory frameworks. Countries with more capacity (i.e. South Africa, Thailand and India) focused their attention on increasing self-reliance and bolstering the private sector. Countries shared the challenges relating to workforce development and retention, local manufacturing, domestic funding for R&D and financing therapy coverage.

Developing, testing and approving gene therapies suitable for LMICs will take decades, providing ample time for countries to chart a path forward. This report shows that while gene therapy should not be a priority area for every country, breaking down infrastructure into component parts helps government leaders create roadmaps for capacity building that align with their country's health, economic and political agendas.

When crafting long-term strategies, policy-makers should avoid the formation of vertical programmes, but instead integrate gene therapy into national and institutional plans, strengthening health systems in the process. Moving forward, policy-makers should form regional and global partnerships to address technological, legal and economic barriers. Such collaborations are crucial for:

- Facilitating knowledge exchange for workforce development and regulatory alignment
- Funding exploratory gene therapy R&D appropriate for LMIC infrastructure
- Designing or offering new manufacturing platforms with more sustainable supply chains
- Improving affordability and coverage through innovative financing

Supporting LMIC R&D, local manufacturing and clinical testing will not only lead to therapies that are safe and effective for local communities but also improve affordability by lowering costs and increasing competition, which will benefit patients globally. The resources necessary to build this capacity will be significant, but if long-term success and health-system strengthening are prioritized, LMICs will not only reap the health and economic benefits but also lead the direction of this field.

1

Introduction

Gene therapies are reshaping modern medicine, but access remains an issue – especially in LMICs.

1.1 The case for gene therapies in LMICs

The ability of gene therapy to create targeted changes in the human genome is opening doors to treating and even curing dozens of life-limiting diseases. Yet the features that make gene therapies novel and transformative also make them difficult to access. To develop, test and administer gene therapies, health systems must be equipped with advanced manufacturing, sophisticated hospital equipment, specially trained personnel and mature regulatory environments.

The necessary infrastructure required to manufacture and deliver gene therapies has contributed to their high price tags. In 2022, Zynteglo, a gene therapy for beta thalassaemia, a rare blood disorder, received regulatory approval in the US with a projected price tag of \$2.8 million for a one-time infusion.³ While prices remain high for now, technological innovation, corporate competition and new payment models are expected to lower costs and improve access to gene

therapies in high-income countries. This is not the case for LMICs, where limitations in R&D, a lack of gene therapy-related healthcare infrastructure, limited trained workforce, insufficient policy and constraints on financing create enormous barriers. These challenges have generated scepticism in scientists, patients and other stakeholders about the long-term feasibility of gene therapies in low-resource settings.

The narrative that new healthcare technologies are unsuitable for LMICs is a long-standing rationale for excluding a majority of the world from the benefits of modern medicine. Without concerted efforts to build gene therapy capacity in LMICs, the global health divide will continue to widen. The gene therapy industry is in its infancy, but early clinical successes and substantial funding have generated enormous momentum. This is an ideal moment for LMICs to enter the global market, prioritizing the needs of communities carrying the highest disease burdens.

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1.2 Using this report

As countries decide whether to invest in gene therapies, they must weigh the future benefits of these potentially curative therapeutics against their direct and indirect costs and the health needs of their citizens. This is a difficult and daunting task, given the fast pace and novelty of the field. Furthermore, the successful build-up of gene therapy capacity, from preliminary R&D to integration within health systems, is contingent upon several interconnected areas (e.g. workforce, financing, policy).

This report aims to simplify and contextualize the global gene therapy landscape, serving as a resource for leaders in government, industry, health systems and civil society interested in building gene therapy capacity in LMICs. First, the report deconstructs gene therapy into seven “capacity pillars”, each providing a concise overview of its role in developing or delivering gene therapies.

Second, the report examines case studies from five LMICs. Each country is actively engaged in developing infrastructure specific for gene therapy, representing different geographic regions and economic stages: upper-middle income (South Africa, Thailand), lower-middle income (India, Tanzania) and low income (Uganda). Additionally, case study countries focus on distinct disease and infection targets, most of which have high prevalence in those regions (Figure 1).

The report concludes with a list of questions designed to help leaders begin building their own roadmap. Recognizing that there is no single correct way forward, each country must consider how investments in gene therapy infrastructure align with their national health, economic and political agendas.

FIGURE 1 | Case study countries and their gene therapy disease target(s)



Uganda	Tanzania	South Africa	Thailand	India
<ul style="list-style-type: none"> – HIV prevalence 5.5% in adults (0.7% global average)¹ – >15,000 babies born annually with sickle cell disease (~300,000 globally)² 	<ul style="list-style-type: none"> – ~11,000 babies born annually with sickle cell disease³ 	<ul style="list-style-type: none"> – 6.7% prevalence of HBV⁴ – 7.2 million people living with HIV⁵ – 24.6/100,000 males born with haemophilia A⁶ 	<ul style="list-style-type: none"> – 3–9% prevalence of beta thalassaemia among newborns⁷ 	<ul style="list-style-type: none"> – More than 1 million new cases of cancer are diagnosed every year (accounting for ~8% of the world's cancer patients)⁸

Notes:

1. Human immunodeficiency viruses (HIV); “Release of Preliminary Results of the 2020 Uganda Population-Based HIV Impact Assessment”, Ministry of Health, press release, 2022.
2. Ndeezi, G., Kiyaga, C., Hernandez, A. G., et al., “Burden of Sickle Cell Trait and Disease in the Uganda Sickle Surveillance Study (US3): A Cross-Sectional Study”, 2016.
3. Makani, J., Tluway, F., Makubi, A., et al., “A Ten-year Review of the Sickle Cell Program in Muhimbili National Hospital, Tanzania”, 2018.
4. Hepatitis B virus (HBV); “National Guidelines for the Management of Viral Hepatitis”, Department of Health – Republic of South Africa, 2019.
5. Allinder, S. M. and Fleischman, J., “The World’s Largest HIV Epidemic in Crisis: HIV in South Africa”, Center for Strategic and International Studies, 2019.
6. South African Haemophilia Foundation: <https://haemophilia.org.za/>.
7. Chaibunruang, A., Sornkayait, K., Chewasateanchai, M., et al., “Prevalence of Thalassemia among Newborns: A Re-visited after 20 Years of a Prevention and Control Program in Northeast Thailand”, 2018.
8. “Patients Are Waiting, for the Revolution”, Immuneel: <https://immuneel.com/the-india-story/>.

Source: Created by Kevin Doxzen for the World Economic Forum

2

Landscape

Gene therapies are being developed to treat and cure a range of diseases, but their value may not reach the countries in which the disease burden is highest.

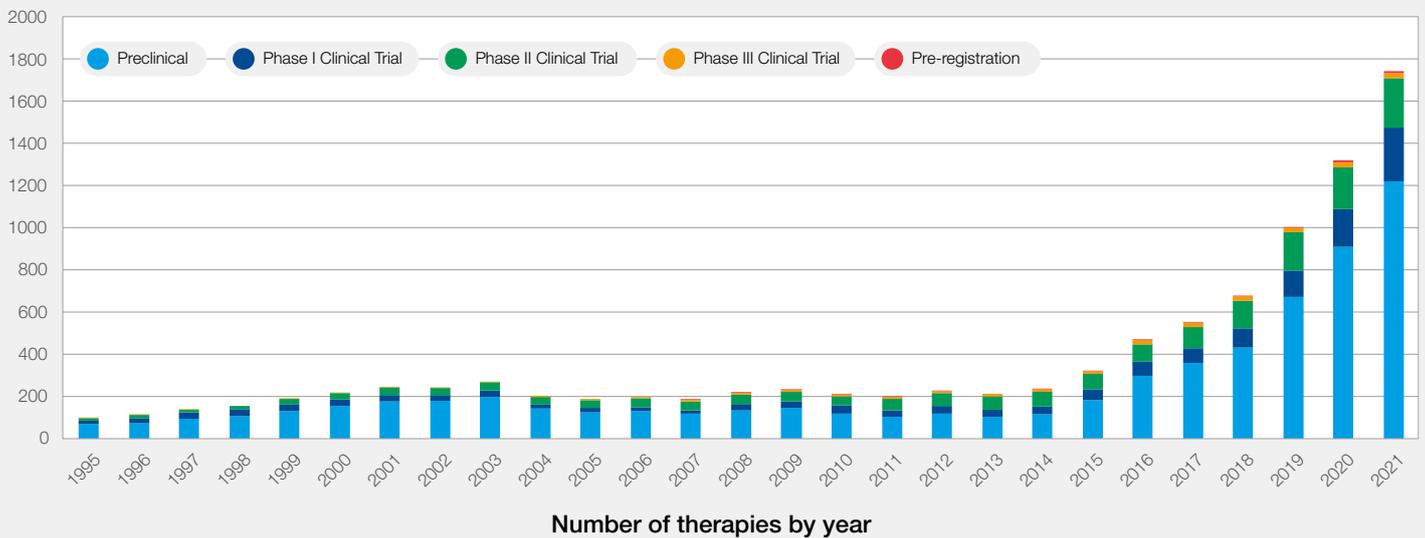
2.1 The rise of gene therapies

Gene therapies represent a new class of medicines. By removing, replacing or inserting genetic material (DNA and RNA) into a patient's cells, gene therapies can treat and potentially cure genetic, infectious and malignant diseases. Unlike traditional medicines that are taken over a person's lifetime and temporarily alleviate symptoms, gene therapies are a one-time procedure offering long-term value.

Gene therapy research and development (R&D) is growing exponentially. In mid-2022, there were

more than 2,000 gene therapies in development, from early-stage research to late-stage clinical testing (Figure 2).⁴ The focus is spread across dozens of therapeutic areas, including cancer, neurological, blood, immunological and cardiovascular diseases. These novel therapies are already changing lives. People living with sickle cell disease, cancers such as leukaemia and lymphoma, and multiple rare diseases have experienced remarkable improvements during clinical trials.⁵

FIGURE 2 Technological innovation has stimulated an exponential rise in gene therapy research



Source: "Gene, Cell, & RNA Therapy Landscape: Q2 2021 Quarterly Data Report", American Society of Gene and Cell Therapy and Citeline, 2021

BOX 1 Defining gene therapies

This report defines gene therapies as the use of genetic material to treat or prevent disease, involving the introduction of a genetic sequence into cells in vivo or ex vivo (Figure 3). While some reports place *CAR chimeric antigen receptor*

modified T cell (CAR-T cell) therapy in a separate "cell therapy" category, this report places it under gene therapy. CAR-T cell therapy uses the genetic alteration of T immune cells to target specific cancers.

2.2 Expectations for innovation and the economy

Technological innovation is improving the safety, efficacy and feasibility of gene therapies. Over the past 10 years, advances in next-generation genetic engineering tools (e.g. CRISPR, base editing, prime editing), declining costs of DNA sequencing and the ability to specifically target cells across the body have combined to make gene therapy one of the fastest-growing areas of medicine.

One area of gene therapy innovation with major implications for affordability and access is the method of administering the therapy (Figure 3). Approximately 73% of gene therapies currently in development use ex vivo delivery, a well-established procedure. Alternatively, in vivo delivery is in the early stages of development, gradually improving safety and efficacy, yet will prove to be more cost effective and is thus the long-term goal for many developers.

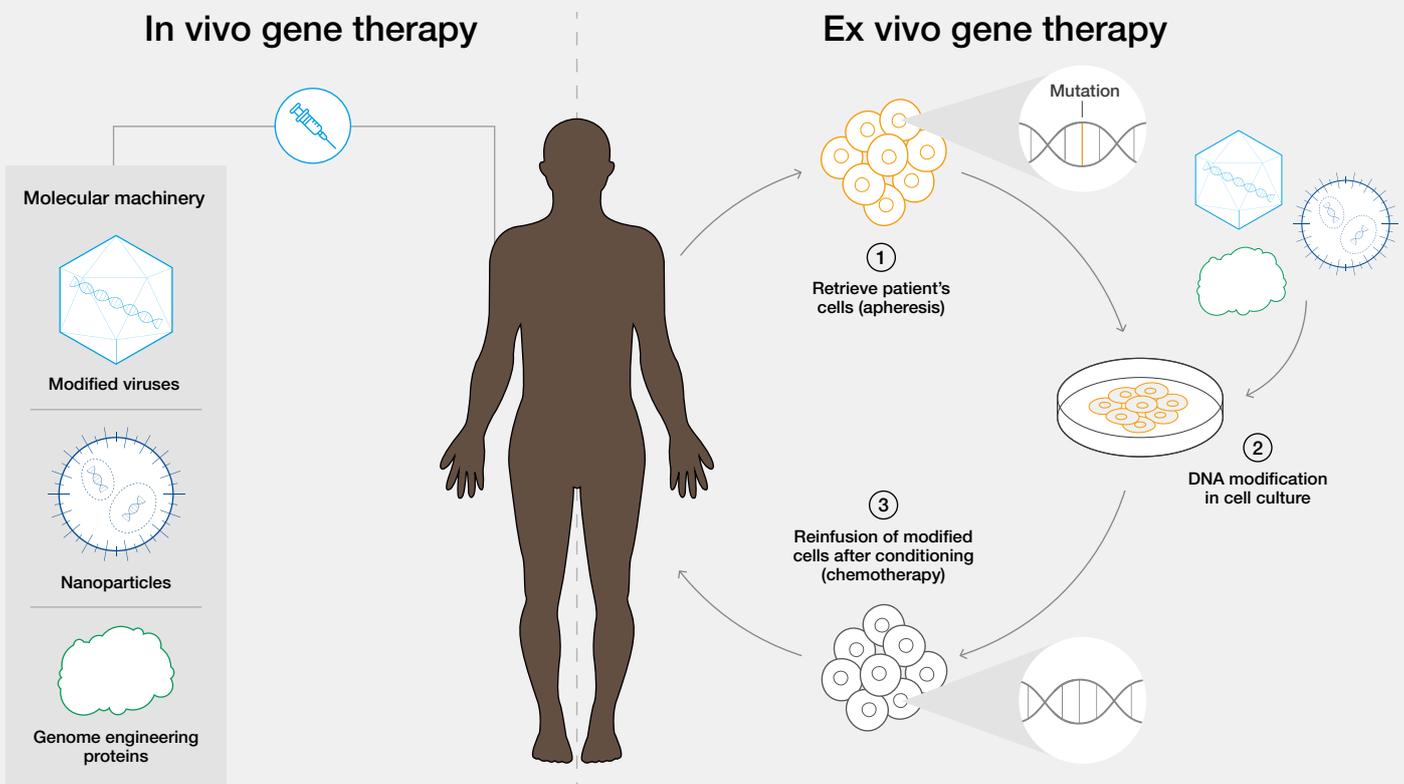
Diversely funded innovation translates into lower costs. While the estimated cost of goods for current in vivo gene therapies ranges from \$100,000 to \$500,000 (Figure 11), industry-led innovation is expected to drive down costs tenfold over the next 10 years. Philanthropic organizations such as the Bill and Melinda Gates Foundation are aiming to achieving another tenfold cost reduction,

down to \$1,000–\$2,000 per dose, which will be required to make in vivo gene therapies cost-effective for LMICs.⁶ Yet, as outlined in this report, a cost-effective cure will remain inaccessible if the correct infrastructure is not in place.

In addition to their impact in healthcare, gene therapies will have considerable economic implications. The global gene therapy market size is expected to grow at a compound annual growth rate of 30.1% from 2022 to 2027.⁷ At this rate, the market is forecast to increase from \$5.33 billion in 2022 to \$19.88 billion by 2027. The customizability of gene therapies to alter a wide range of DNA sequences for treating or curing dozens of diseases creates significant market growth opportunities in the near future.

Durable gene therapies have the potential to provide substantial net savings for health systems. In the US, a gene therapy for haemophilia is projected to yield per-patient lifetime cost savings of \$6.8 million.⁸ Net long-term savings by different gene therapies will vary across health systems, affected by the specific disease target, standard-of-care costs, the ages and number of patients and other factors.

FIGURE 3 Methods of administering gene therapies



Caption: In vivo – introducing gene therapy molecular machinery into a patient's body to genetically alter specific cells. Ex vivo – removing a person's cell, creating the intended genetic alteration, and reintroducing the altered cells back into the patient.

Source: Created by Kevin Doxzen for the World Economic Forum

2.3 A widening global gap

“ While clinical research remains limited to HICs, LMICs carry nearly 90% of the global disease burden.

Despite the immense global health and economic potential of gene therapies, innovations and access to these technologies remain concentrated in high-income countries. In the US, more than 60 gene therapies are expected to receive approval by 2030, while estimates suggest more than 1 million patients will receive treatment by 2034.^{9,10} This level of access to gene therapies will not be the reality for most of the world. In 2022, of the 20 approved gene therapies worldwide, only three were approved in LMICs (China, Brazil and the Philippines).¹¹

In countries without approved products, the main access point to gene therapies is currently through clinical trials. In August 2022, there were approximately 1,000 open gene therapy clinical trials (including CAR-T) globally, yet fewer than 5% were recruiting in LMICs (not including China), with only four trials in Africa.¹²

Neither the health benefits nor the economic benefits of a growing gene therapy market are reaching LMICs. In 2021, developers raised a record \$22.7 billion, driven by venture capital and up 57% from two years prior, but much of this investment stayed in HICs.¹³ Of the 1,308 developers worldwide working on gene therapy and related technologies, the vast majority are based in high-income regions. Only seven developers operated in South America and 22 in the Middle East and Africa. While this is consistent with the global distribution of pharmaceutical companies, supporting innovation in LMICs will help create technologies fit for resource-constrained settings.

While clinical research remains limited to HICs, LMICs carry nearly 90% of the global disease burden.¹⁴ In order to develop gene therapies that are safe and effective for populations in LMICs, clinical trials must be performed in those countries. Since biological and genetic diversity varies widely across populations, countries cannot rely solely on gene therapies developed and tested abroad. Reaching this goal will involve supporting locally led clinical trials and attracting international pharmaceutical companies to partner with LMICs. This has historically been difficult due to long trial application processes, lack of regulatory experience and political buy-in, and low profitability potential.

Building gene therapy capacity in LMICs will also provide value to patients globally. The gene therapy field is at a critical point, where innovation in diagnostics, manufacturing, therapeutic delivery and other areas of technology are improving affordability. The type of innovation necessary to implement gene therapies in LMICs will lower costs and increase competition, creating positive spillover effects for health systems globally.

Closing the global gap and realizing the value of gene therapies in LMICs is a multi-decade endeavour, raising the imperative to take immediate steps towards capacity building. Understanding where and how to begin starts with untangling requisite gene therapy infrastructure into component parts to assess current country capabilities and develop a long-term strategic roadmap.

BOX 2 What is a cure?

Gene therapies are often described as “cures”, yet they may not completely eradicate a disease for the duration of a person’s lifetime. A therapy’s efficacy may vary between individuals due to biological, environmental or social factors. During the development and testing stages, stakeholders

(e.g. pharmaceutical companies, regulators, end users, donors and members of civil society) work together to agree upon definitions (e.g. what is meant by “cure”), which influence how gene therapies are approved by regulators, covered by insurers and perceived by patients.

BOX 3 Why use gene therapy when there are cheaper alternatives? An HIV case study

In 2021, approximately 38 million people worldwide were living with human immunodeficiency viruses (HIV), with 67% residing in sub-Saharan Africa (SSA).¹⁵ While antiretroviral therapy (ART), the current standard of care, has drastically increased life expectancy, it alone will not stop the epidemic. Many people living with HIV are unable to access effective treatment/medication, while 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 from AIDS worldwide. An HIV cure would obviate the current requirement for long-term

administration of ART, improving the quality and quantity of life.

A gene therapy “cure” for HIV would either control the virus (remission) in the absence of any ongoing treatments such as ART, or completely remove the infectious active virus (eradication) from the body. The Gates Foundation is leading an effort to develop a \$1,000–\$2,000 gene therapy cure, a cost-effective price point for LMICs. A study of four low and lower-middle income countries in SSA calculated an average facility-level ART cost of \$208 per patient-year, adding up to \$4,160 over 20 years.¹⁶

3

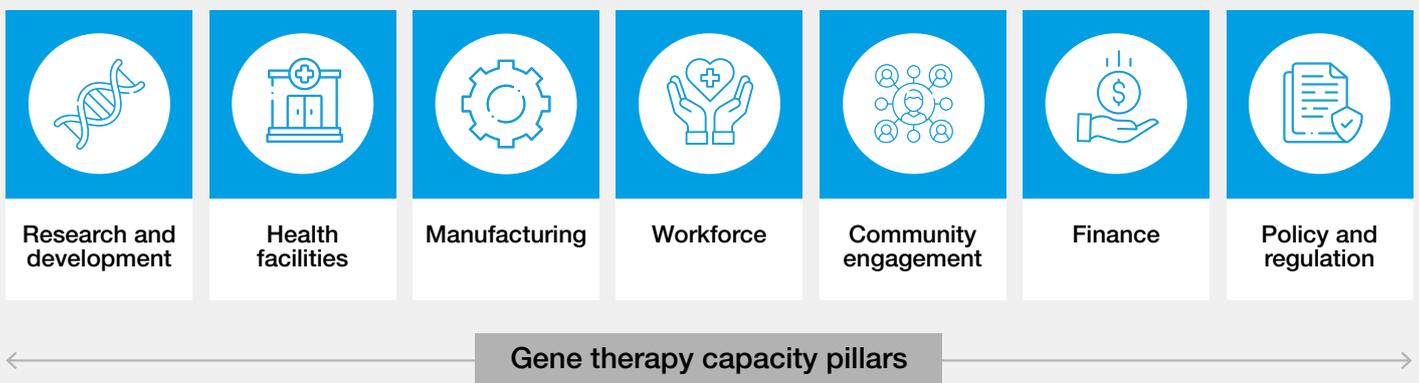
Capacity pillars

What are the core components for sustainable development and delivery of gene therapies?

The long-term viability and impact of gene therapies within LMICs is contingent upon the support and attention given to each of the capacity pillars below (Figure 4). While this list is not comprehensive, these seven areas warrant explicit attention,

recognizing that they are not independent but deeply interconnected. This chapter provides a brief overview of each pillar, describing its role in gene therapy development and delivery as well as considerations for LMICs.

FIGURE 4 Gene therapy capacity pillars



Source: Created by Kevin Doxzen for the World Economic Forum

3.1 Research and development

A strong research and development (R&D) ecosystem, with synergy between academia and industry, is central to the long-term affordability, sustainability and health impact of gene therapies. While participation in international gene therapy

research is essential for LMICs with limited R&D infrastructure, building a robust in-country and regional R&D ecosystem that can support technology development and clinical testing is the long-term goal for creating LMIC self-reliance.

The gene therapy R&D ecosystem

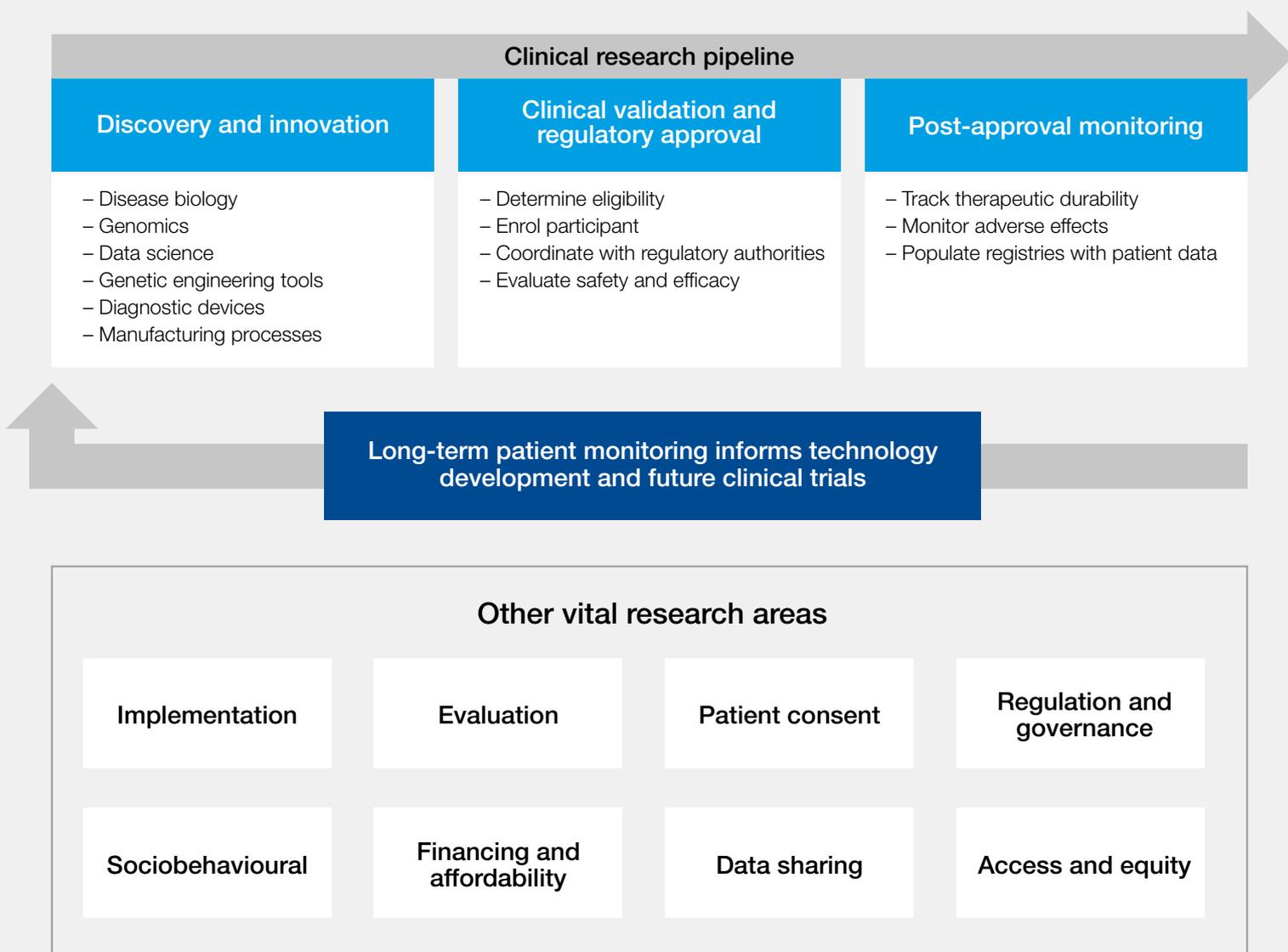
At its core, gene therapy is an advanced medical technology created via a multistep clinical research pipeline: discovery and innovation, clinical validation and regulatory approval, and post-approval monitoring (Figure 5). This is an iterative process in which long-term patient data will guide the development of new technologies, eventually lowering costs and opening the door to treating a wider range of diseases.

All case study countries have initiated the discovery and innovation stage, either at select academic institutions (e.g. Tanzania’s Muhimbili University of Health and Allied Sciences [MUHAS] and Uganda’s

Joint Clinical Research Centre) or in the private sector (e.g. Genepeutic Bio and Immuneel Therapeutics) while only South Africa, India and Thailand have begun clinical testing (e.g. gene therapies for haemophilia, beta thalassaemia and leukaemia).

Creating an accessible and acceptable gene therapy involves more than clinical research. In tandem with building the clinical pipeline, focus must be directed at additional research areas, including implementation practices, sociobehavioural studies, novel financial models and ethical data sharing.

“ LMICs can take a systems approach to integrate gene therapy R&D capacity within their national and institutional health, education and economic strategies.



Source: Created by Kevin Doxzen for the World Economic Forum

Building blocks for R&D success

Integration in national and institutional strategies

– LMICs run the risk of establishing gene therapy as a vertical programme that deliberately bypasses local systems seen as ineffective. Instead, LMICs can take a systems approach to integrate gene therapy R&D capacity within their national and institutional health, education and economic strategies. National strategies (e.g. Thailand 4.0) formalize commitments to areas of innovation, while institutional strategies (e.g. the Tanzania Sickle Cell Institute) operationalize capacity development by facilitating multidisciplinary and multisector collaboration, coalescing a diversity of research and healthcare activities, and simplifying funding streams.

Balanced funding streams – multiple funding streams contribute to R&D capacity, the makeup

of which influences research priority areas, ownership of intellectual property, and ability to disseminate and implement research findings. For example, philanthropic funding can catalyse LMIC research in higher-risk and exploratory areas, while national government initiatives are better positioned to support long-term R&D infrastructure development.

Strengthening intellectual property protections

– international and domestic companies are more likely to invest in emerging research areas such as gene therapy if there are strong IP regimes in place.¹⁷ Enforcing patents will require robust legal systems and may be facilitated by creating a supranational patent court system to distribute costs over a region.

3.2 Health facilities

“ A well-designed hub-and-spoke network promotes resource conservation, return on investment, service excellence and enhanced market coverage.

Delivering gene therapy requires a core set of specialized equipment housed within larger hospitals that can provide acute care. As these facilities receive funding to conduct clinical trials, coordinated networks must be formed to ensure

that patients are appropriately educated, screened and monitored at primary or secondary health facilities before and after their gene therapy treatment within tertiary health centres.

Creating networks for advanced care

Proposed “hub-and-spoke” models are designed to coordinate comprehensive care by dividing gene therapy services between a central facility (“hub”) experienced in both comprehensive care and gene therapy, and secondary establishments (“spokes”) that offer limited services and act as the home centres for patients (Figure 6).¹⁸ Such a network-based model leverages existing health infrastructure (e.g. community services for screening) and uses a referral system among primary-, secondary- and tertiary-level facilities. These models offer quality care to patients who are geographically dispersed, minimizing the need for frequent long-distance travel to advanced hospitals.

Hubs – tertiary care facilities

Hubs serve three core functions: research and academic activities; coordinating and administering gene therapy; and ensuring patient safety before and after treatment.

A rate-limiting factor for establishing and sustaining hubs is the installation and ongoing financing of specialized equipment. Building off existing infrastructure can help overcome this hurdle. For example, ex vivo gene therapy involves much of the same infrastructure used for bone marrow transplants/haematopoietic stem cell transplant (referred to here as BMT). BMT capacity varies widely across LMICs, but can be used as a proxy to help identify potential hubs for gene therapy.

BOX 4 Bone marrow transplants across LMICs

Countries such as Tanzania and Uganda are beginning to invest in advanced therapies, building in parallel the infrastructure for multiple complex procedures as part of updated institutional health strategies.

Uganda: The Joint Clinical Research Centre aims to carry out the country’s first bone marrow transplant (BMT) by the end of 2022.¹⁹

Tanzania: In 2021, Muhimbili National Hospital conducted Tanzania’s first BMT, making Tanzania the third country in Africa with transplant units. Across the continent, Nigeria conducted a BMT for

sickle cell disease (SCD) and recently established its own centre.²⁰

Conversely, countries such as South Africa and India are building gene therapy capacity on the back of decades of advanced medical infrastructure.

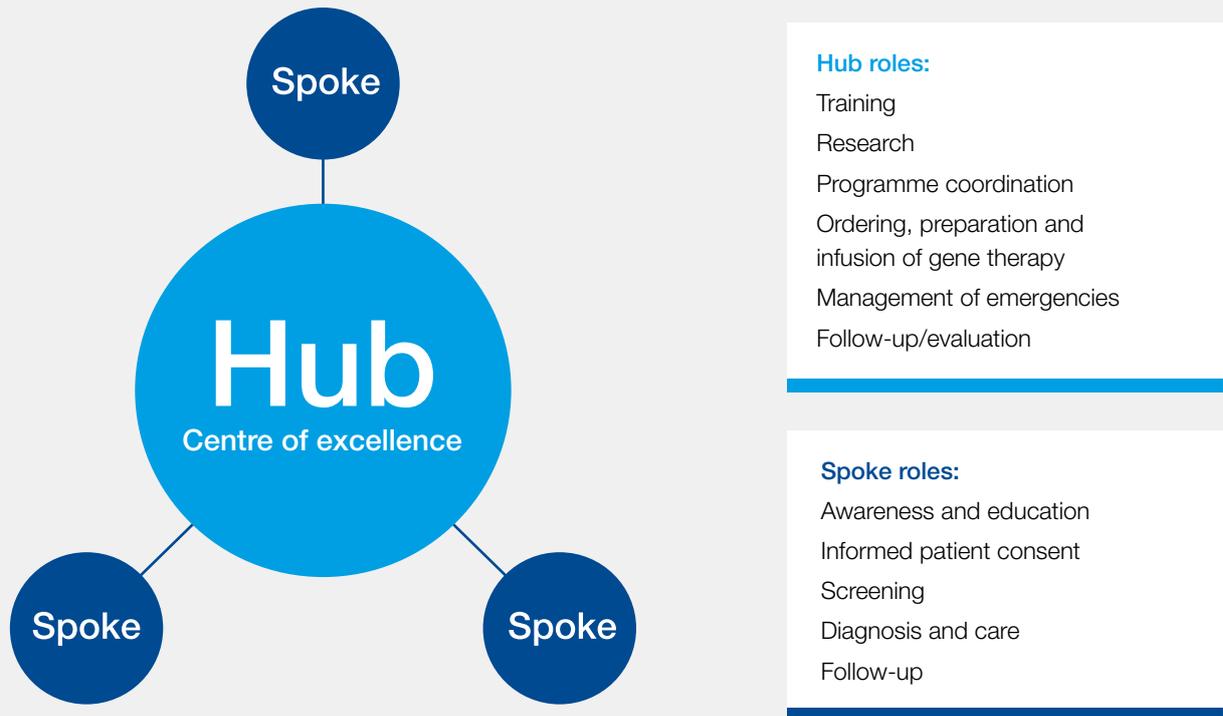
South Africa: South Africa performed its first BMT in 1976 and, by 2017, the country was performing approximately 425 transplants per year.²¹

India: In 2018, there were 65 BMT centres in India reporting data to the Indian Stem Cell Transplant Registry.²²

Spokes – primary and secondary care facilities

Funding and focus can gravitate solely towards hubs such as centres of excellence, yet resourcing primary and secondary care facilities to serve as spokes is necessary to improve patient access. Spokes serve three core functions: engaging and educating communities and prospective patients;

screening individuals eligible for gene therapy; and carrying out long-term follow-up sessions to track physical, mental and emotional health. As safety and efficacy improve and gene therapy transitions from ex vivo to in vivo delivery, tasks performed solely in hub centres may shift to spokes.



Caption: A well-designed hub-and-spoke network promotes resource conservation, return on investment, service excellence and enhanced market coverage.¹

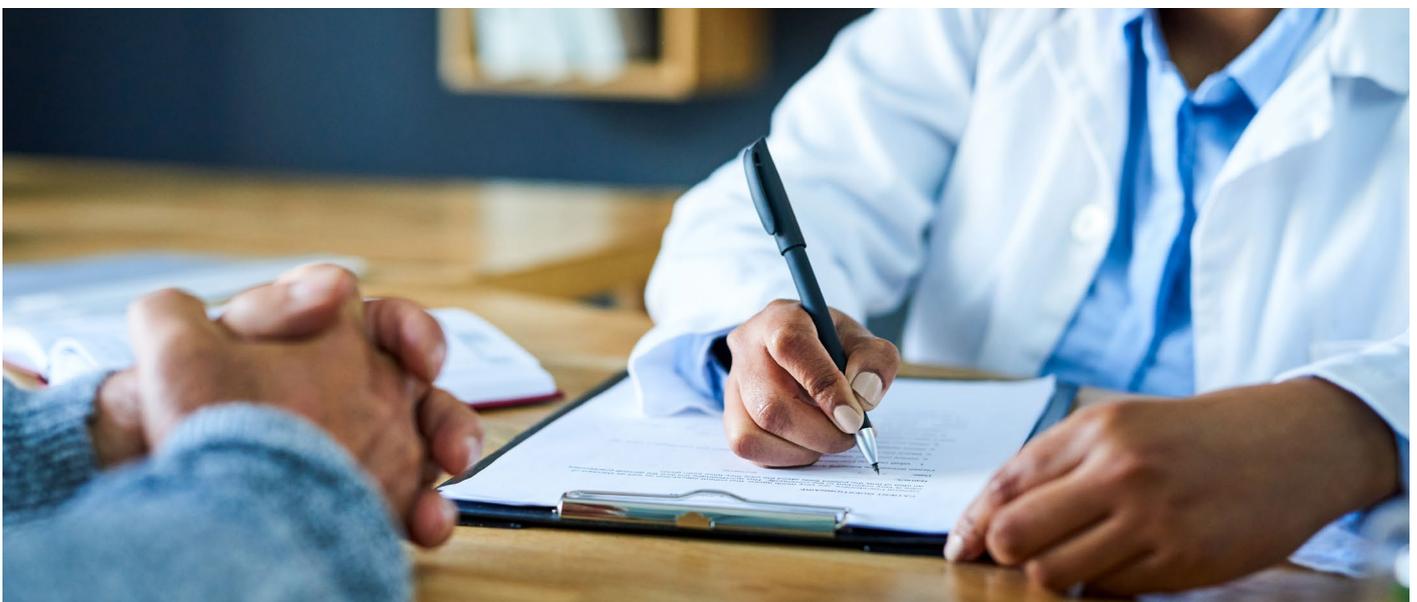
Source: Created by Kevin Doxzen for the World Economic Forum

Note: 1. Elrod, J. K. and Fortenberry, J. L., "The Hub-and-Spoke Organization Design: An Avenue for Serving Patients Well", 2017.

BOX 5 | The essential role of registries

As patients move between hubs and spokes, data should be collected and stored in registries (e.g. the World Federation of Hemophilia Gene Therapy Registry, SickleInAfrica registry) to inform the best possible care. This data also serves vital research purposes by informing the design of clinical trials

and acting as a platform for long-term follow-up. When establishing and governing registries, stakeholders must determine who has access, how to protect patient privacy and how patient advocacy groups, industry, governments, academia and professional societies can collaborate.

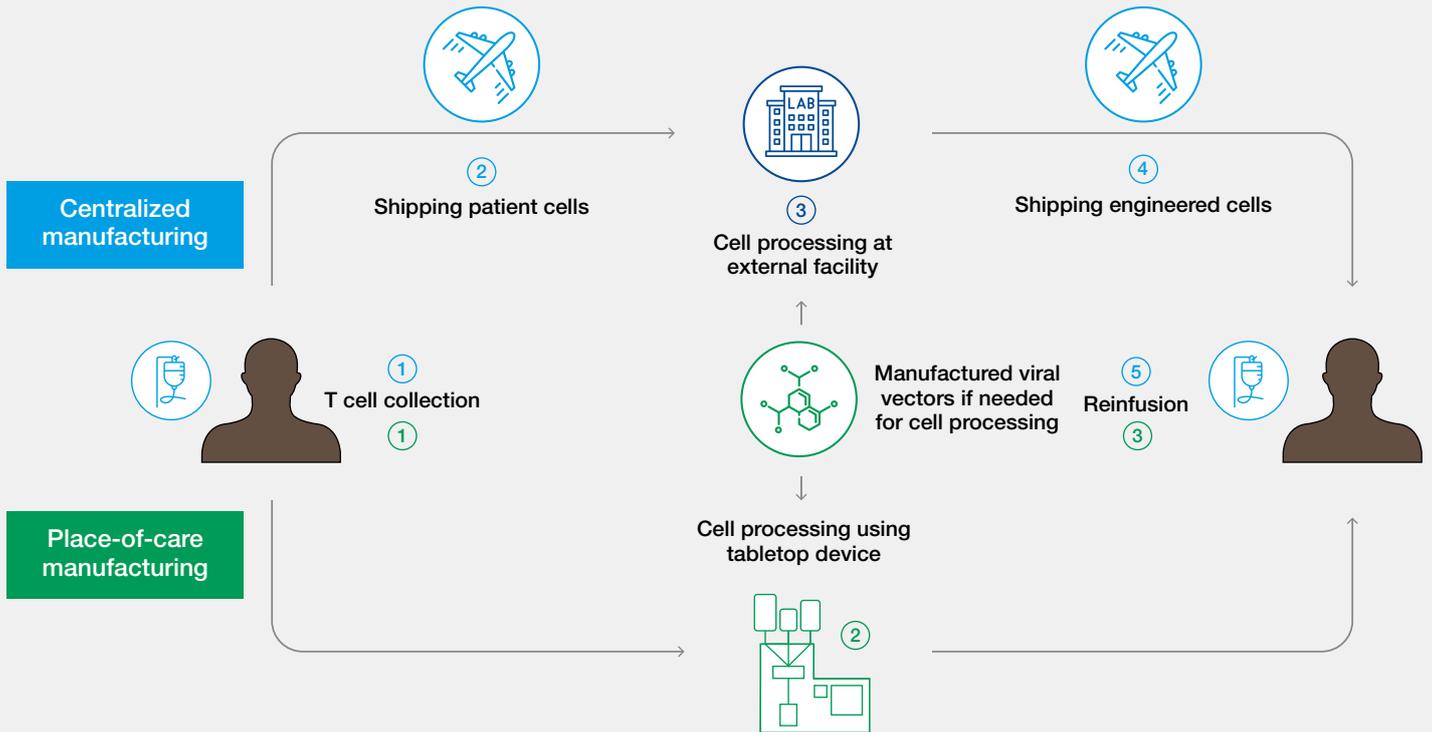


3.3 Manufacturing

Gene therapy manufacturing is more complicated than producing small molecules or antibodies due to the use of living cells and viral vectors.²³ Complex supply chains involve a wider diversity of stakeholders, closely coordinating the extraction, genetic alteration and reinfusion of patient cells. Additionally, regulation requires strict quality control and traceability along the supply chain.

These factors create significant barriers to entry when building in-house manufacturing capacity, meaning that LMICs must begin developing long-term strategies. This necessitates balancing near-term needs that may require outsourcing to HICs with long-term goals of building domestic capacity that will eventually lower costs and achieve self-reliance.

FIGURE 7 Improving access through place-of-care manufacturing



Caption: Centralized manufacturing, currently the primary manufacturing method for ex vivo gene therapy, involves complex cold chains and advanced tracking and logistics. Place-of-care manufacturing will lower costs and simplify processes by keeping manufacturing within treatment centres.

Source: Created by Kevin Doxzen for the World Economic Forum

Engineering patient cells

The cost of goods for gene therapy ranges from \$100,000 to \$500,000 per patient in HICs (Figure 11). Two critical steps overwhelmingly contribute to this cost and are key focus areas for innovation:

- **Delivery vehicles:** Viral vectors, special types of inactive viruses, are currently the most common vehicles for delivering genetic material into cells. They were used in almost 70% of clinical trials in 2019, but scaling their production remains an issue as early manufacturing processes required hundreds of millions of litres of cell culture to create enough material to treat 1,000 patients.^{24,25} Viral vectors will eventually be replaced by faster, cheaper and easier-to-manufacture delivery vehicles for in vivo and

ex vivo gene therapy. LMICs must play an active role in the development, testing and monitoring of next-generation delivery vehicles to optimize their manufacturing and handling within LMIC settings and ensure they are safe for the intended patient population.

- **Cell processing:** For ex vivo therapy, patient cells are removed from the body and processed (i.e. genetically engineered) using viral vectors or other delivery mechanisms. This is done at either a designated external facility (centralized manufacturing) or at the local treatment facility (place-of-care manufacturing), a decision that significantly affects accessibility for LMICs, as discussed in the next section.

“ Place-of-care manufacturing could reduce the number of trained people needed roughly fivefold and shorten the procedure by weeks.

Closer is better for LMICs

There is a global shortage of gene therapy manufacturing capacity, particularly for viral vectors. Estimates suggest hundreds of new facilities will need to be built simply to meet the demand for currently approved therapies.²⁶ The COVID-19 pandemic has spurred global efforts to build capacity for biomanufacturing in LMICs, which countries such as South Africa intend to use for gene therapy purposes in the future.²⁷

Reaching a cost-effective price point requires place-of-care manufacturing (Figure 7). While centralized manufacturing acts as a stopgap as LMICs conduct clinical trials, the labour, logistics and shipping costs associated with this approach are unsustainable and unscalable. Instead, place-of-care manufacturing could reduce the number of

trained people needed roughly fivefold and shorten the procedure by weeks.²⁸

In preparation for a clinical trial, Christian Medical College in Vellore, India, demonstrated the feasibility and reliability of place-of-care manufacturing for CAR-T cells, while the Joint Clinical Research Centre in Uganda is exploring mobile cleanrooms as a way to engineer cells locally.^{29,30}

Ownership of manufacturing materials and technologies also affects access and costs. LMICs can either license viral vector and cell-processing technologies from academic institutions or companies in HICs at an affordable price (e.g. Caring Cross model) or develop their own indigenous (in-country) technologies.

3.4 Workforce

Large youth populations within LMICs present an opportunity to reimagine a future workforce that drives innovation, improves societal health and grows new markets. Gene therapies can be part of this vision. As the industry matures and continues

to thrive, candidates will want to pursue careers in this space, making LMICs a hub for innovation and gene therapies a catalyst for economic growth. This process begins with understanding the entirety of the gene therapy workforce.

The multifaceted gene therapy workforce

Supporting gene therapy requires the establishment of new positions and the upskilling of current roles, enabling the development of other capacity pillars. A diverse workforce will be needed across multiple

disciplines: research, healthcare, community engagement, finance, policy and regulation, and manufacturing (Figure 8).

FIGURE 8 Gene therapy demands workforce development across multiple disciplines





“ The WHO recommends one clinical haematologist per 100,000 people in every country. South Africa has fewer than one per 2 million, while many other countries in sub-Saharan Africa have even fewer.

Balancing supply and demand

The World Health Organization estimates a projected shortfall of 15 million health workers by 2030, mostly in LMICs. The WHO recommends one clinical haematologist per 100,000 people in every country. South Africa has fewer than one per 2 million, while many other countries in sub-Saharan Africa have even fewer.³¹ **The introduction of gene therapy could stretch already overworked medical specialists such as haematologists, oncologists and immunologists, who are necessary for delivering gene therapy cures for sickle cell disease (SCD), haemophilia, HIV and cancer.**

Once initial investments are made to train a skilled healthcare workforce, countries must secure their employment, which is a nuanced process. In some countries and states, trained doctors are absorbed into health systems, while in other locations, public and/or private hospitals and clinics lack the resources to hire highly trained staff. Pharmaceutical companies and other private-sector industries also play a role in providing career opportunities for trained workers. Without career opportunities, skilled workers are likely to migrate to HICs, resulting in “brain drain”.

Upskilling and lifelong learning

Gene therapy is a rapidly evolving field, making it difficult for health professionals to stay abreast of regulatory changes, technological advances and clinical opportunities. **Collaborative education and training programmes, often organized by professional societies, serve the purpose of upskilling professionals and sharing best practices by drawing on international and public-private partnerships.** For example, the International Society on Thrombosis and Haemostasis launched an education initiative, Gene Therapy in Hemophilia, targeting clinicians with the aim of improving understanding of the fundamentals of gene therapy, the treatment approach, research and clinical trials, safety and efficacy outcomes, and how to identify patients who could benefit.

The unique safety risks, complex manufacturing practices and alternative payment and financing

models associated with gene therapies will demand a skilled regulatory workforce. Agencies including the South African Health Products Regulatory Authority (SAHPRA), the Fundisa African Academy of Medicines Development and the African Union Development Agency are working together to improve capacity-building programmes for African regulators.³²

Manufacturing has been reported as the skill area of greatest concern globally. Small batch sizes, personalized products and high quality standards make gene therapy manufacturing slow and labour-intensive. In the United Kingdom alone, the workforce will need to double from 3,000 in 2019 to 6,000 by 2024 to meet demand.³³ While certain biomanufactured materials should be exported to LMICs, local manufacturing will be necessary to reduce costs, requiring a skilled local workforce.

3.5 | Community engagement

FIGURE 9 Integrating community voices to develop better therapies



Source: Created by Kevin Doxzen for the World Economic Forum

Patients, caregivers and advocates must be included throughout the R&D process to help shape research design, care implementation and policy development and ensure that a safe and effective cure meets the needs of the whole patient (e.g. physical, mental, emotional) and their communities (e.g. economic, social).

Proper community engagement involves respect, mutual understanding, integrity, transparency, accountability and community autonomy.³⁴ A critical tool for achieving these goals are community advisory boards (CABs), comprised of community representatives who voice the concerns and interests of communities, particularly during the design and execution of clinical research.³⁵ CABs also create educational resources that are culturally attuned, up-to-date and comprehensible to their communities. Gene therapy engagement activities in Uganda for HIV and in Tanzania for SCD serve as exemplars for connecting with communities early and often.

By participating in the design and execution of research, service implementation and policy formation, communities can improve (Figure 9):

- **Acceptability:** Does the proposed therapy address the clinical problem ethically and effectively and suit an individual's lifestyle (e.g. culture, beliefs and daily activities)?
- **Accountability:** Are researchers, policy-makers, industry leaders and funders fulfilling their commitments and working together to meet the needs of patients?
- **Affordability:** Are financing plans in place to ensure all patients can receive treatment?
- **Accessibility:** Have all barriers (financial, political, geographical) to access been considered and appropriately addressed?

Engagement topics for gene therapy

Patient and community engagement is critical for awareness, understanding and improved effectiveness in all areas of healthcare. In gene therapies, a unique degree of emphasis is needed regarding topics related to:

- **Altering DNA:** Changing a person's genetic code can touch on spiritual and religious questions in a way that is different from other forms of health intervention. Proper engagement must manage expectations (e.g. the idea of a magical cure) and address misinformation tied to genetically modified organisms (GMOs) or human embryo editing.
- **Clinical trial enrolment:** Enrolling patients into gene therapy clinical trials is contingent upon informed patient consent. Effective education and engagement are critical to enrolling diverse cohorts, but can be difficult, given the uncertainty about gene therapy safety and efficacy and the treatment's scientific complexity.³⁶
- **Long-term monitoring:** To fulfill regulatory requirements, implement payment and reimbursement plans and iteratively improve R&D, patients must be monitored for several years post-treatment. Engagement is needed to support patients mentally, emotionally and financially over this period.



3.6 Policy and regulation



In personalized therapies – cell therapies, gene therapies and neoantigen therapies – a patient is not just the recipient of a drug product. The patient is the product.

Vineti blog, 30 May 2019

The unique nature of these personalized treatments makes them difficult 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.³⁷ 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 separate frameworks.³⁸

Regulatory challenges

The novelty and long-term durability of gene therapies has created uncertainty for regulators. While ensuring patient safety is the primary concern, regulators want to create systems that can

efficiently evaluate therapeutic efficacy and promptly deliver cures to waiting patients. To achieve this goal, several regulatory challenges need to be overcome (Figure 10):

“Frequent and reliable communication between researchers and regulators is critical to provide timely guidance, prevent misunderstanding and share lessons learned.”

- **Site selection:** Factors impacting the location and number of clinical trial sites include clinical experience, capacity to receive and store gene therapy materials, and ability to coordinate and manage patients, which may require cross-border enrolment.
- **Chemistry, manufacturing and controls (CMC):** Variability in starting materials and complex manufacturing processes create challenges for ensuring quality and consistency.
- **Types of assessments:** Gene therapy studies require a variety of simple and complex evaluations, necessitating decisions on who is qualified to perform them, how frequently they need to be performed, and where they can be performed.
- **Novel endpoints:** In clinical trials, “surrogate endpoints” are used as signs to determine if a therapy is working rather than waiting to observe lifelong benefits.

- **Long-term monitoring:** Altering DNA can lead to unexpected adverse effects, which is why the US Food and Drug Administration (FDA) recommends at least 15 years of follow-up after product administration.³⁹

Frequent and reliable communication between researchers and regulators is critical to provide timely guidance, prevent misunderstanding and share lessons learned.⁴⁰ The use of informal regulatory meetings, such as the FDA’s INTERACT meetings, provide opportunities for communication in the early stages of gene therapy R&D and should be considered as a model as LMICs establish regulatory systems. Early and continued communication also eases the challenges of long-term patient monitoring by addressing funding difficulties, accelerating the entry of gene therapies in healthcare markets and confronting ethical data-sharing questions.

Promoting convergence

Differences in regulatory frameworks between countries make it difficult for gene therapy developers to design their clinical programmes. Navigating different timelines, documentation requirements and study requirements ultimately impedes market access, even among experienced countries.⁴¹ Improving global access will require the convergence of regulatory requirements and technical standards.

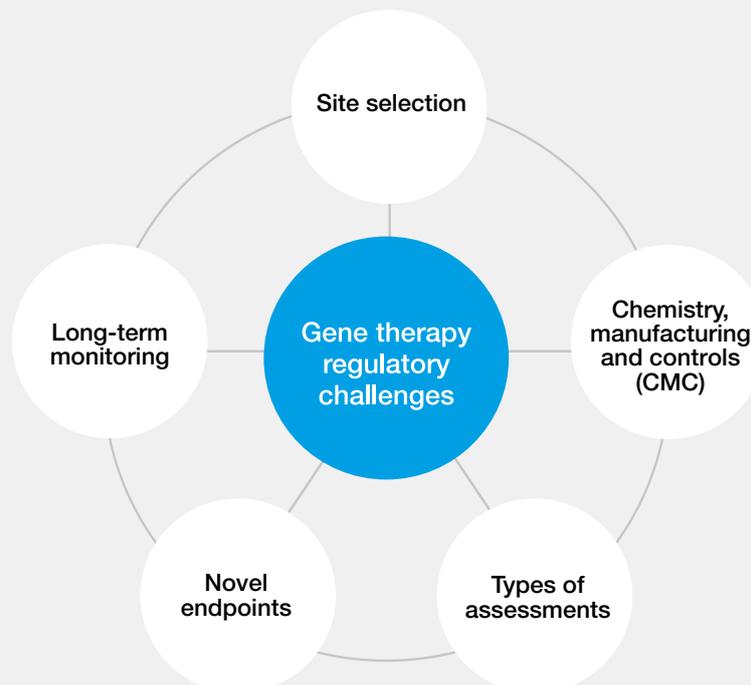
The World Health Organization (WHO) is playing a leading role in this effort, publishing a draft

consideration on regulatory convergence of cell and gene therapy products.⁴² The WHO is also working with Uganda to develop a model framework that can be used by other LMICs.

Sharing tasks among national regulatory authorities (work-sharing) and recognizing assessments performed by other authorities (reliance) can help expedite access to gene therapies in lieu of complex regulatory frameworks.

FIGURE 10

Key challenges for gene therapy regulatory frameworks



Source: Created by Kevin Doxzen for the World Economic Forum

3.7 Finance

A roadmap without funding is just a vision. Operationalizing strategies for capacity development requires a combination of funding streams, while achieving market penetration and patient access in LMICs involves creative financing mechanisms.

When making financial decisions to improve technology innovation and access in LMICs, stakeholders must strive for local ownership, learning from past experiences in which outside investments have led to vertical and isolated programming that is not aligned with country priorities.

Driving innovation through synergistic funding

Economic projections suggest that industry-led innovation will reduce the costs of an in vivo gene therapy cure for HIV to \$10,000–\$50,000/dose in HICs over the next 10 years, which may result in a price of \$50,000–\$100,000/dose in HIC markets. In comparison, an HIV cure would need to cost and be priced at \$1,000–\$2,000 in LMICs to be cost-effective (Figure 11).

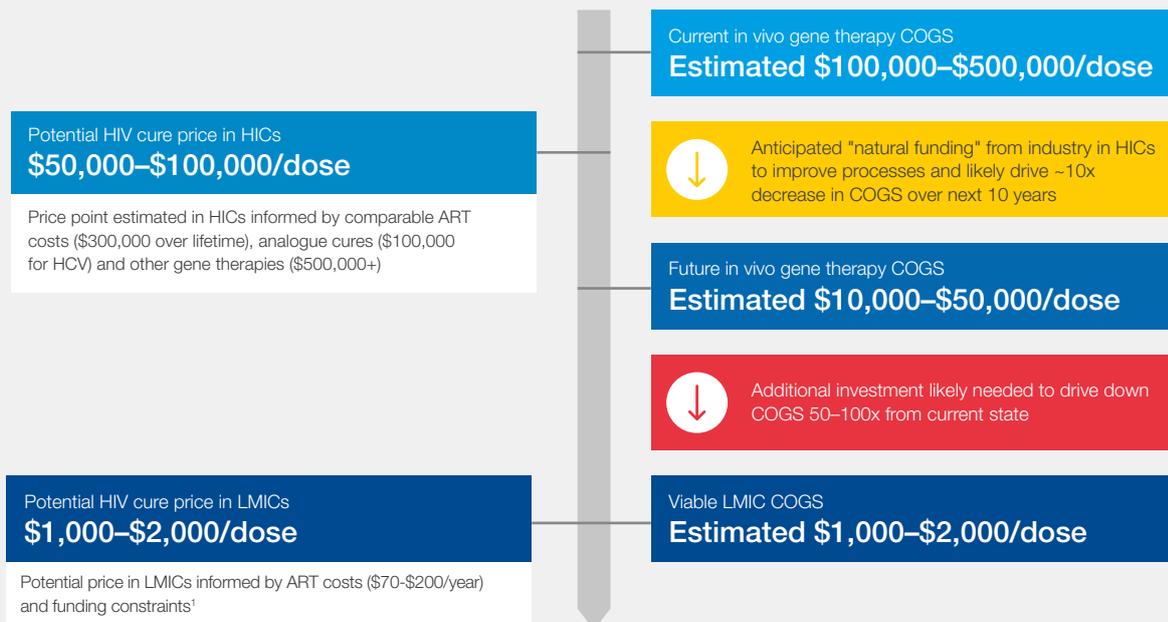
Additional investments are needed to close the innovation gap. Philanthropy plays an essential role by funding high-risk research designed for LMICs from the outset. This is exemplified by the Bill and Melinda Gates Foundation's collaboration with the US's National Institutes of Health (NIH), Novartis and other companies to develop single-shot cures for HIV and SCD.⁴³

Frameworks on intellectual property and technology transfer that promote LMIC innovation and local production will help to lower costs further. Non-profits and benefit corporations, which are not beholden to profit-maximizing objectives, play a critical role in this area.

While focus on technology development is integral to achieving cost-effective gene therapies that target specific diseases, funders should not overlook investments in workforce development, community engagement and other essential activities. These are areas in which LMIC governments should play primary roles as funders or in funding decisions due to the horizontal nature of these investments and their alignment with national plans.

FIGURE 11 Market insights and why philanthropic funding is needed

Estimating current “cost of goods” (COGS) and potential COGS reduction



Note: Assumes 5–10 years of durable remission, lowest possible price of therapy must be comparable with ART costs excluding treatment costs (no discounting); see Phillips, A. N., Stover, J., Cambiano, V., et al., “Impact of HIV Drug Resistance on HIV/AIDS-Associated Mortality, New Infections, and Antiretroviral Therapy Program Costs in Sub-Saharan Africa”, 2017.

Source: Boston Consulting Group directional analysis based on expert interviews (n=8), Gerson Lehrman Group market report



Improving access through creative financing

Cost-effectiveness does not guarantee access to gene therapies. These costly procedures must be conscientiously incorporated into public insurance schemes, particularly as LMICs strive towards their universal health coverage goals. While this may be a challenging prospect for countries such as India where out-of-pocket expenses accounts for ~62% of total health expenditure, other countries such as Thailand already cover stem cell transplants.⁴⁴

Through public-private partnerships, countries can negotiate financing models that fit the patient population:

- **Voluntary licensing:** Licences are given in part or full for the production and distribution of a product (e.g. manufacturing and importing low-cost HIV drugs in sub-Saharan Africa).⁴⁵
- **Donation programmes:** Treatment is provided for free via volume donations to patients if access is not affordable (e.g. World Federation of Hemophilia improving access to care in 112 countries).⁴⁶
- **Value-based tiered pricing:** The price a country pays is commensurate with the local value it provides.⁴⁷
- **Subscription models:** Countries or regions pay fixed amounts for access to drugs for patients who require access (e.g. the Australian government paying upfront for hepatitis C treatment for all affected citizens).⁴⁸

BOX 6

The role of health technology assessments

Health technology assessments (HTAs) help determine whether the price of health interventions reflects their benefit to patients. The multimillion-dollar price tag of gene therapies in HICs has made HTAs an essential tool in setting coverage policies, and will be critical for LMICs as they

negotiate financing models. While some LMICs have already institutionalized HTAs (e.g. Thailand, Colombia, Brazil and India), others are seeking guidance from the global advisory group Health Technology Assessment International (HTAi), the WHO and other international groups.⁴⁹

The next section provides case studies on how LMICs are establishing and implementing these pillars, contextualizing the role gene therapies could serve in addressing high-burden diseases. The diverse economic and political realities across

countries means that certain pillars pose more immediate challenges and require targeted action and partnerships to enable progress. These early-adopting countries offer learnings for other countries seeking to develop gene therapy roadmaps.

Case studies

How are countries actively building gene therapy capacity to address high-burden diseases?

Case studies from five LMICs were selected to capture a wide breadth of gene therapy readiness. The order of countries roughly aligns with increasing readiness. This section presents key enablers that expedite capacity building, which other countries can

adopt to advance their gene therapy programmes. Additionally, critical challenges impeding gene therapy research and commercialization were identified, suggesting where immediate steps should be taken to prevent bottlenecks in capacity building.



CASE STUDY 1

Uganda



Uganda aspires to change the narrative around delivering innovative healthcare technologies in low-resource settings. By 2024, Uganda aims to launch its first gene therapy clinical trial, targeting one of two high-burden diseases – human immunodeficiency viruses (HIV) and sickle cell disease (SCD).

- At the end of 2020, an estimated 0.7% of adults aged 15–49 years were living with HIV worldwide.⁵⁰ In Uganda, the prevalence of HIV in the same age group was approximately 5.5%.⁵¹
- As for SCD, Uganda is among the countries with the highest disease burden in the world. In 2015, the global estimate of newborn children with SCD was 300,000, with >15,000 born in Uganda.⁵²

Uganda intends to conduct a proof-of-concept clinical trial at the Joint Clinical Research Centre (JCRC) in Kampala. This will establish Uganda as a regional leader, creating a model for infrastructure and policy readiness.

Enablers

- **Public-private partnerships** – Uganda has formed strategic partnerships to address capacity gaps across workforce development, hospital infrastructure, technology transfer and regulation. For example, the Gates Foundation is providing funds to train researchers and build place-of-care manufacturing.

- **International regulatory guidance** – the WHO is supporting Uganda as a case study for building and adopting a regulatory and governance framework for gene editing, which will serve as a benchmark for other LMICs.

Challenges

- **Limited infrastructure** – the JCRC aims to carry out the country's first bone marrow transplant by the end of 2022.⁵³ While this is a significant step towards enabling advanced medical procedures, additional capacity (e.g. manufacturing, quality control testing) is needed to conduct a clinical trial for ex vivo gene therapies.
- **Inadequate policy** – Uganda currently lacks a regulatory framework for gene therapies. Legislators plan to update the Genetic Engineering Regulatory Act to address gene therapy research and clinical validation.
- **Minimal government investment** – in 2014, Uganda spent 0.14% of GDP on R&D (basic and applied research across disciplines), among the lowest on the continent.⁵⁴ Similarly, the number of researchers in Uganda (26.5 per million) is significantly lower than the African average (95.1 per million).⁵⁵



CASE STUDY 2

Tanzania

Tanzania has developed a model that integrates gene therapy into a comprehensive healthcare delivery system, ensuring that the right patients receive the right care at the right time. The country is taking this holistic approach to address one of the country's most pressing, yet globally under-resourced, health burdens – SCD – which the Ministry of Health has made a disease of national priority.⁵⁶

- SCD is the leading genetic cause of mortality in children in Africa. 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 rates of the disease.^{57,58}

Tanzania has engaged stakeholders, including patient communities, healthcare providers and researchers, and formed national, African and international partnerships to build the infrastructural, regulatory and workforce capacity to launch a gene therapy clinical trial for SCD. MUHAS is one of the key institutions leading efforts through its sickle cell programme, which is also developing other advanced SCD interventions including bone marrow transplants and exchange blood transfusions.

Enablers

- **Supporting the patient journey** – Tanzania is strategically investing in patient-centred approaches, establishing medical camps for health education, building dedicated sickle cell clinics for patient referral and creating a patient registry for those eligible for advanced therapy.⁵⁹ Organizations such as the Tanzania Sickle Cell Disease Alliance, the National Noncommunicable Disease and Injury

- (NCDI) Poverty Network, the NCD Alliance Engagement and other entities lead community engagement and support activities, characterized by weekly meetings, and quarterly and annual events.

- **Scaled networks** – for SCD, Tanzania is forming or participating in research and implementation networks at the institutional (MUHAS sickle cell programme), national (national sickle cell programme), regional (REDAC – Sickle Cell Disease Research Network Africa), African (Sickle Cell Pan-African Network – 17 countries) and global levels (Global Gene Therapy Initiative). In genomics, the country has formed the Tanzania Genome Network and Tanzania Society of Human Genetics, and is using established networks such as H3Africa.

Challenges

- **Technology development and transfer** – knowledge exchange and commercialization are priorities for the national government, but institutions lack technology transfer capacity and only five patents were granted to residents between 2011 and 2020.⁶⁰
- **Training and retaining researchers** – Tanzania has 18.3 researchers per million people, which is far below the African average. Some 71.3% of researchers are employed by higher education while 28.7% are employed by the government, indicating limited opportunities for private-sector employment.⁶¹





CASE STUDY 3

South Africa



South Africa is a hub for life sciences research. In 2013, South Africa had 91% (345) of Africa's internationally accredited laboratories.⁶² This established academic infrastructure is being deployed to develop gene therapies for hepatitis B viral (HBV) infection, HIV and haemophilia.

- Approximately 257 million people live with chronic HBV infection worldwide, with an estimated 6.1% prevalence (60 million) in sub-Saharan Africa and roughly 6.7% prevalence in South Africa (3.4 million).^{63,64}
- An estimated 7.2 million South Africans live with HIV (19% prevalence among adults), accounting for 20% of all people living with HIV globally.⁶⁵
- The prevalence of haemophilia, a rare genetic blood disease, is evenly distributed worldwide. In South Africa, an estimated 24.6/100,000 males are born with haemophilia A and 5.0/100,000 males with haemophilia B. Disease management is heavily skewed, with quality of life reduced by 64% in upper-middle income counties, by 77% in middle-income countries and by up to 93% in low-income countries.⁶⁶

Based out of the University of the Witwatersrand, the Antiviral Gene Therapy Research Unit (AGTRU), an extramural research unit of the South African Medical Research Council (SAMRC), is in the basic research phase of HBV gene therapy development. Similarly, the Institute for Cellular and Molecular Medicine (ICMM), also an SAMRC extramural research unit, based at the University of Pretoria, is researching gene therapy for HIV.

While there are no South African-led clinical trials, researchers at the University of the Witwatersrand have experience and expertise in clinical trial research, participating in several ongoing global haemophilia clinical trials.⁶⁷

Enablers

- **Hub-and-spoke model for patient care** – haemophilia gene therapy has served as an ideal case study for designing hub-and-spoke models for care management.⁶⁸ South Africa has followed suit, with haemophilia treatment centres referring patients to a single advanced hospital for gene therapy infusions.⁶⁹

- **Production hubs** – in South Africa, the private sector and government have partnered with academic centres to establish a facility to produce and distribute locally developed vaccines for Africa-specific COVID variants.⁷⁰ The long-term intention is to repurpose the facilities to manufacture other curative therapies, including gene therapy.
- **Building a clinical-scientist workforce** – the government of South Africa is closing the workforce gap through the Bongani Mayosi National Health Scholars Program (BM-NHSP), a recent initiative launched by the National Health Research Committee (NHRC), in partnership with South African Medical Research Council (SAMRC), National Department of Health (NDoH) and Public Health Enhancement Fund (PHEF). The BM-NHSP aims to train at least 1,000 PhD students in health and clinical research within a decade.

Challenges

- **Manufacturing infrastructure and regulation** – there is currently no gene therapy manufacturing in South Africa. Establishing a central facility will require government investments. As for regulation, South Africa has a regulatory and research ethics framework, allowing gene therapy clinical trials in the country, yet there is no framework for regulating gene therapy manufacturing.⁷¹
- **Healthcare inequality** – with a Gini index (measurement of a country's wealth distribution) of 63 in 2021, South Africa is considered the most unequal country in the world.⁷² While 16% of the population is served by private healthcare, 84% receives resource-limited public care.⁷³ Plans to develop a South African national health insurance scheme must consider access to future gene therapies.
- **Few specialists in public sector** – in 2019, South Africa had approximately 17 specialist doctors for every 100,000 people, far below the Organisation for Economic Cooperation and Development (OECD) country average of 274.⁷⁴ There were 69 specialists for every 100,000 patients in the private sector and only seven in the public sector. Investments in training gene therapy specialists must be combined with incentives to practise in the public sector.



CASE STUDY 4

Thailand

Like South Africa, Thailand has built a robust R&D ecosystem, but unique to this South Asian country is its dynamic academic-industry networks. Thailand is eager to transition to a knowledge economy, becoming a regional innovation hub by training scientists and facilitating employment in industry jobs.

Thailand is using its R&D capacity to develop gene therapy cures for two prominent diseases.

- Beta thalassaemia, a genetic blood disease, has a 3–9% prevalence among newborns in Thailand⁷⁵
- Acute lymphoid leukaemia (ALL), a rare cancer of the blood and bone marrow, primarily affecting children

Efforts to develop gene therapy products are under way in at least three major medical universities in Thailand, with varied degrees of international collaboration with the US and Europe and within Asia. Funded by bluebird bio, a US pharmaceutical company, research at Thailand's Ramathibodi Hospital, Mahidol University, is part of an international gene therapy clinical trial for beta thalassaemia.⁷⁶ The product is already approved in Europe and is awaiting Thai government approval. By 2023, researchers hope to treat ALL using CAR-T cell therapy based on technology developed in Thai academic centres⁷⁷ and licensed to Genepeutic Bio, a local pharmaceutical company, for manufacturing.

Enablers

- **Government coverage of advanced therapies** – patients undergoing haematopoietic stem cell transplants receive ~\$21,000 before treatment and up to one year after transplantation for ongoing treatment and monitoring.⁷⁸ If gene therapy becomes cost-effective, advocates are hopeful that the Thai government will provide coverage.
- **National strategy for R&D** – out of all case study countries, Thailand has the highest ratio of R&D to GDP at 1.14%. Through the new 20-year national strategy called Thailand 4.0, the government aims to increase R&D to 4%, with a focus on biotechnology and medical technology. The Eastern Economic Corridor will help reach this goal by evolving into a medical hub and potentially housing large pharmaceutical facilities.

Challenges

- **Untested regulation** – Genepeutic Bio will be the first company to submit a clinical trial application to the Thai Food and Drug Administration. Current regulation of gene therapies is insufficient to address manufacturing, quality assurance and long-term surveillance, but regulators are aligning with frameworks in the US, EU, Japan and Australia.
- **Shortage of venture capital (VC)** – VC has been instrumental in financing gene therapy start-ups in HICs. Finding VCs who are willing to invest in uncertain technologies coming out of inexperienced entrepreneurial ecosystems is a difficult task. Thailand's creation of science parks is designed to streamline fundraising activities and launch new companies.





CASE STUDY 5

India

India has sufficient capacity across R&D, medical infrastructure and regulation to disrupt the global gene therapy market. Government, physicians and industry leaders intend to achieve this goal by developing indigenous technology that could drastically lower costs. One area of immediate clinical interest is treating haematological malignancies (blood cancers that begin in the bone marrow or immune system).

More than 1 million new cases of cancer are diagnosed every year in India, accounting for approximately 8% of the world's cancer patients.⁷⁹ Scarce access to advanced interventions has resulted in high mortality rates. CAR-T cell therapy represents the latest advanced cancer treatment, yet a single infusion in the US costs between \$375,000 and \$475,000.⁸⁰ India has the potential to reduce this cost tenfold over the next few years using local manufacturing.⁸¹

The CAR-T landscape across India is highly active, with academic trials approved at the Tata Memorial Centre Advanced Centre for Treatment, Research and Education in Cancer in partnership with the Indian Institute of Technology Bombay, and at the Christian Medical College in Vellore. Pharmaceutical companies are nearing the clinical testing phase using their own technologies.

Enablers

- **Decentralized manufacturing** – researchers at the Christian Medical College in Vellore demonstrated the feasibility of decentralized (place-of-care) manufacturing to create

CAR-T cells within a hospital setting rather than shipping a patient's cells to a central facility.⁸² This would dramatically reduce costs, increase speed and improve access.

- **Advanced health facilities** – in 2018, there were 65 stem cell transplant centres in India reporting data to the Indian Stem Cell Transplant Registry.⁸³ These advanced facilities could be fitted to administer gene therapies in the future.
- **Appropriate regulatory oversight** – India has a robust regulatory ecosystem with multiple bodies overseeing gene therapy research and clinical trials. In particular, the Gene Therapy Advisory and Evaluation Committee of the Indian Council of Medical Research advises on trial design and safety.

Challenges

- **Geographic disparities** – most of India's advanced medical facilities are located within urban areas, yet the vast majority of India's population live in rural areas (close to 75%). Promoting access will mean equipping rural clinics with gene therapy capacity through hub-and-spoke models and/or assisting patients to reach urban facilities.
- **Insufficient workforce** – India has only 16 skilled health workers per 10,000 population, falling short of the WHO's minimum of 22.8.⁸⁴ Projections suggested a need for more than 5,000 oncologists in 2020, yet a 2018 survey estimated that there were only 1,500 in the country.⁸⁵ Gene therapy may continue to strain this burdened workforce.



Despite challenges, the above countries are finding different ways to advance gene therapy, given their political and economic constraints. Models that combine political will, international partnerships and system-strengthening enable sustainable

capacity building within resource-limited settings. Using lessons learned from these case studies, the following section lists critical questions that countries need to consider before constructing their own gene therapy roadmaps.

Questions

By answering key framing and priority-setting questions, government leaders can begin the deliberative process of constructing an ambitious yet realistic gene therapy roadmap.

There is no generalized pathway for sustainably building gene therapy capacity. Instead, each country must develop its own roadmap, a process that begins with objective-setting. Government leaders must assess their priorities and determine whether investments in gene therapy programmes will benefit the population, considering both the practical and ethical factors. Reaching this decision requires multistakeholder engagement and cooperation across government agencies, sometimes resulting in the formation of separate committees.

As demonstrated in the case studies above, focusing on specific disease areas helps focus the conversation and provides a nucleus around which partnerships can form, infrastructure can be built and regulatory systems can be tested, before expanding to other diseases. After identifying a particular health need that a gene therapy programme could address, government leaders should answer the following questions to begin building their country-specific roadmap.

Who? – achieving accessibility and acceptability through partnerships and forecasting

- Who are the international, national and institutional champions motivated to propel gene therapy?
- Who are the potential liaisons within communities and among advocacy organizations?
- Who will benefit (or not) from gene therapies and how will global trends (e.g. social, environmental) play a role?
- Who will fill future workforce needs and who will provide training and knowledge exchange?

What? – filling capacity gaps with key infrastructure, regulation and financing

- What equipment is required for clinical trials and eventual scaling?
- What regulatory gaps and barriers are hindering research and commercialization?
- What is preventing gene therapy from being cost-effective and what financing mechanisms can improve access?

When? – discerning the right time for gene therapy

- When will gene therapy investments be appropriate, given the current political and economic climates?
- What high-burden diseases could gene therapy feasibly treat or cure now and in the future?
- What are the benefits of early adoption (e.g. regional competitiveness)?
- What are the benefits of late adoption (e.g. using established models)?

Where? – locating eligible patients and building networks of care

- Where are the communities with the highest disease burden and how can they be reached?
- Where should health facilities (hubs and spokes) be built to maximize patient reach and care?
- Where should manufacturing infrastructure be focused (central vs. decentralized)?

Why? – building an argument for advanced therapies

- Why would gene therapy investments benefit patients, communities and society?
- Why do converging trends in funding, public health and technological innovation provide the basis to warrant investment in gene therapy?
- Why should public funding go to gene therapy research?

How? – strategically charting a path forward

- How can gene therapy support health system strengthening and how will success be evaluated?
- How can private-sector growth and indigenous technology development be encouraged?
- How can external funding spur research innovation and lead to self-reliance?
- How can gene therapy help achieve the United Nations sustainable development goals (SDGs) and universal health coverage (UHC) goals?

Conclusion

This report is part of a broader movement to build gene therapy capacity in LMICs, driven by global partnerships and disruptive thinking.

The pressure to adopt advanced medical technologies can prevent investment in other more cost-effective health interventions. Understanding the value that a long-lasting treatment such as gene therapy can provide to individual patients and society is vital for countries in determining if, how and when gene therapies may fit within their national agendas.

The case studies chosen for this report demonstrate the unique role that gene therapies play in addressing high-burden diseases. While some countries have chosen to be early adopters of this technology, establishing regional competitiveness, others will wait to learn from regional partners who are creating capacity-building models.

Now is the time for conversations about securing long-term access to the economic and public health benefits of gene therapies in LMICs. Gene therapy is at an inflection point. Decades of exploratory research have laid the foundation for powerful new technologies, leading to roughly 1,000 clinical trials and substantial private-sector growth. This report makes the case that not only can LMICs enter the global market, but their inclusion is critical

for improving patient access worldwide. Finding ways to manufacture and administer gene therapies in resource-constrained settings will lead to more affordable technologies and processes. Using this innovation to treat patients in high-burden disease areas safely and effectively means performing clinical trials in LMICs, taking into account the vast biological diversity within these countries.

Achieving this goal will require new research and financing models that cater for low-resource settings and are unconstrained by profit-maximizing paradigms. This can be made possible through public-private partnerships, commitment from LMIC governments and engagement with patients and communities.

A mixture of infrastructure must be in place to take gene therapies from preliminary R&D through clinical testing all the way to market access. Creating a sustainable pipeline involves understanding how these pieces interconnect, which this report attempts to articulate. By providing a brief overview of what is required to deliver gene therapies in LMICs, along with real-world examples, this joint project by the World Economic Forum, Thunderbird School of Global Management and Sandra Day O'Connor College of Law at Arizona State University adds to the growing movement eager to bring the benefits of gene therapies to millions of individuals around the world.

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Acknowledgements

We would like to thank members of the Sickle Cell Advanced Therapy Programme at Muhimbili University of Health and Allied Sciences for their insight: Daima Bukini, Agnes Jonathan, Eka Patricia Kisali, Winnie Lema, Frederick Luoga, Lucio Luzzatto, Grace Moshi, Siana Nkya, Aisha Rifai, Florence Urio, Mohammed Zahir.

Members of the Global Gene Therapy Initiative participated in initial interviews and influenced the content and structure of the white paper.

Editing and feedback was provided by Diana Bowman, Genya Dana, Cameron Fox, Elissa Prichep and Landry Signé.

Editing by Alison Moore, Astra Content. Design and layout by Sophie Ebbage, Studio Miko.

Endnotes

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