

https://dspace.org/

Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa and India

Kenneth Cornetta; Martin Bonamino; Johnny Mahlangu; Federico Mingozzi; S Rangarajan ...

https://hdl.handle.net/10539/36667
WOS

Downloaded from a DSpace repository. https://dspace.org/

Please cite this article in press as: Cornetta et al., Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.04.002

Molecular Therapy
Review

Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India

Kenneth Cornetta,[1] Martín Bonamino,[2,3] Johnny Mahlangu,[4] Federico Mingozzi,[5] Savita Rangarajan,[6] and Jayandharan Rao[7]

[1]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN 46202, USA; [2]Molecular Carcinogenesis Program, Research Coordination, National Cancer Institute (INCA), Rio de Janeiro, Brazil; [3]Vice-Presidency of Research and Biological Collections (VPPCB), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil; [4]Department of Molecular Medicine and Haematology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [5]Spark Therapeutics, Philadelphia, PA 19104, USA; [6]Faculty of Medicine University of Southampton, UK & KJ Somaiya Super Speciality Hospital and Research Centre, Mumbai, India; [7]Department of Biological Sciences and Bioengineering, Indian Institute of Technology Kanpur, Kapur, UP, India

Gene and cell therapies for a variety of life-limiting illnesses are under investigation, and a small number of commercial products have successfully obtained regulatory approval. The cost of treatment is high, and clinical studies evaluating safety and efficacy are performed predominately in high-income countries. We reviewed the current status of gene and cell therapies in low- and middle-income countries and highlighted the need and current barriers to access. The state of product development in Brazil, South Africa, and India is discussed, including lessons learned from American Society of Gene and Cell Therapy (ASGCT)-sponsored virtual symposia in each of these countries.

INTRODUCTION

The first individual to receive gene-modified cells under an approved clinical trial was treated in 1989.[1] Now, over three decades later, we see the promise of genetic therapies becoming a reality for individuals suffering from life-limiting illnesses. The European Union and seven other countries have one or more approved gene therapy products. The number is expected to proliferate, with over 60 new approved products anticipated by 2030.[2] Enthusiasm for these new treatments is well warranted, but worldwide access presents a number of challenges. Here we compare current gene therapy development efforts with major health priorities in under-resourced areas. We then contrast gene therapy needs with access to gene therapy clinical trials and licensed products. Discussions of insights from recent American Society of Gene and Cell Therapy (ASGCT)-sponsored symposia in Brazil, South Africa, and India are used to formulate conclusions and opportunities to foster improved access to novel gene therapies.

BARRIERS TO GENE THERAPY IN LMICs

The current cost of licensed gene therapies is a challenge for high-income countries (HICs) and will make widespread availability in low- to middle-income countries (LMICs) all but impossible. For example, Glybera, the first gene therapy approved in Europe, was priced at €1 million and was later withdrawn because no country provided coverage because of the cost.[3,4] The cancer immunotherapy chimeric antigen receptor T cell (CAR-T) product Kymriah was initially priced at $475,000,[5] and Zolgensma for spinal muscular atrophy was the most expensive drug ever placed on the market with a price of $2.125 million.[6] Cost is not the only challenge for improving access. Many LMICs lack the population health infrastructure available in HICs. For example, newborn screening is not available in many LMICs.[7,8] Similarly, cancer screening is not part of many health systems. Electronic medical record systems are just being developed, and laboratory diagnostics are often limited.[9,10] Standard-of-care treatment, if available, is usually concentrated in urban areas. Individuals' preferences for herbal medications and spiritual healing, lack of medical literacy at the individual and local healthcare provider level, and fear of the diagnosis are also factors that delay diagnosis and treatment.[11,12] Failure to allow the process to be developed locally may limit attempts to bring a new technology forward.

IS THERE A NEED FOR CANCER GENE THERAPY IN LMICs?

Approximately two-thirds of gene therapy clinical trials target cancer.[13] Worldwide, about 70% of cancer deaths occur in LMICs. According to GLOBOSCAN 2020 data, the number of new cancer cases in medium human development index (HDI) countries is predicted to increase by 64% from 2020 to 2040. In low HDI countries, the increase is expected to be 95%.[14] This compares with an anticipated rise of 32% in very high HDI countries. Beyond incidence, individuals with cancer in LMICs have a markedly poorer outcome because of late presentation related to limited knowledge of warning signs, cancer screening, delayed access to care, limited available therapies, and,

https://doi.org/10.1016/j.ymthe.2022.04.002.

Correspondence: Kenneth Cornetta, Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN 46202, USA.
E-mail: kcornett@iu.edu

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article in press as: Cornetta et al., Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.04.002

Table 1. Gene Therapy Trials (accessed November 22, 2021 in ClinicalTrials.gov) by region and by World Bank Income rating

	Studies by geographic region	Total sites open by geographic region
United States and Canada	131	418
Europe	57	106
East Asia	21	22
Australia	17	21
Middle East	8	11
South America	7	7
Japan	3	3
Central America	2	2
Russia	1	1
Africa	1	1

World Bank income	Number of sites
High	562
Upper middle	30
Lower middle	0
Low	0
Upper middle income	**Number of sites**
China	16
Brazil	6
Turkey	4
Bulgaria	1
Columbia	1
Jamaica	1
South Africa	1

The cost and clinical infrastructure required to deliver gene therapies will be a major challenge to providing treatment to individuals in under-resourced areas. The ASGCT Global Outreach Committee has sought to better understand potential barriers and approach to access in three middle-income countries: Brazil, South Africa, and India.

in some cases, a higher prevalence of infectious diseases and other co-morbidities.[12,15–17] The need for novel cancer therapies is growing. Whether they should be a healthcare priority will be discussed under Conclusions.

ARE GENE THERAPIES FOR NON-CANCER DISORDERS RELEVANT IN LMICs?

The greatest number of gene therapy products under development target autosomal recessive diseases. Although individually rare, the number of diseases is large, with the incidence of a single-gene disorder estimated at 3.6 per 1,000 live births.[18] Developing therapies for rare diseases is a financial challenge for any country, given the low number of affected individuals and the high cost of development and regulatory approval.[19] One genetic disorder of particular relevance to LMICs is sickle cell anemia (SCA). This disease is associated with severe pain, organ damage, and a high incidence of early mortality before age 5.[20] The number of individuals with SCA worldwide is predicted to rise by 30% by 2050.[21] When looking at where individuals with SCA reside, over 5 million live in Africa, and another 1 million live in India.[22] In contrast, an estimated 140,000 live in the United States and Europe. As of November 23, 2021, ClinicalTrials.gov (searching for "gene therapy" and "sickle cell disease") listed 18 trials in the United States, one in France, and a United States trial with a site in Jamaica. There were no open clinical trials listed for SCA in Africa or India. In terms of progress in SCA gene therapy, two early studies using lentiviral transduction of hematopoietic stem cells demonstrated control of the disease. In contrast, serious adverse events have been reported in two individuals enrolled in an ongoing industry-sponsored trial.[23–25] One individual treated with CRISPR-Cas9 editing has shown clinical improvement.[26] Both approaches require a clinical infrastructure similar to that used in hematopoietic stem cell transplantation (apheresis centers, regulated cell processing facilities, liquid nitrogen storage, and skilled clinical units), an infrastructure not present in many LMICs.

Gene therapy for hemophilia, a congenital severe bleeding disorder, is an active area of clinical development. The World Foundation of Hemophilia (WFH) has documented limited availability of coagulation factors in many LMICs, resulting in high morbidity and mortality.[27] One of the few phase III gene therapy trials with global participation evaluated *in vivo* administration of an adeno-associated virus vector for hemophilia B. The study is now closed to accrual and is presumably under regulatory review. The study promoted the First WFH Gene Therapy Round Table, which noted several issues to facilitate access.[28] First, LMICs will likely need international support for the vector and its distribution. The group advocated for all phase III studies to use standard endpoints and develop a core dataset to promote review by regulators and payors. Given frequent co-morbidities in LMICs, the group advocated for efficacy studies in "less ideal" individuals. The group also recommended an international registry to monitor efficacy and safety. Interestingly, the potential for an unintended negative effect on LMICs was also raised. Specifically, successful implementation of gene therapy in HICs could weaken global support efforts that currently fund or advocate for hemophilia care in LMICs.

Gene therapy for infectious diseases is another area of relevance to LMICs. HIV is a challenge for many LMICs in terms of prevalence and the need for life-long therapy. The 12 countries with the highest prevalence of HIV are LMICs, with a range of 4.7%–26.8% of the adult population infected.[29] The burden of other communicable diseases remains highest in LMICs. It is largely responsible for the high childhood mortality, which can range from 25 to more 100 deaths per 1,000 live births in some countries.[30] The need to improve healthcare for children is a particularly pressing issue for Africa. Although the population growth in most of the world is predicted to level off by 2050, Africa is the exception. Some investigators indicate that in 2100, 50% of the world's children will be born in Africa. The continent's population will have tripled from today.[26,27] Whether gene therapy will be a significant factor in controlling communicable

Please cite this article in press as: Cornetta et al., Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.04.002

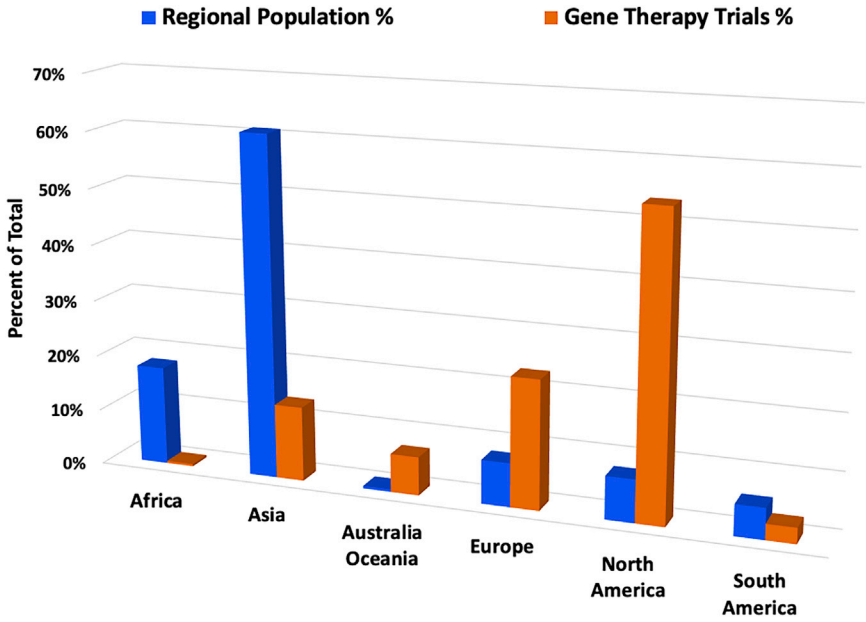

Figure 1. Global gene therapy trial distribution
The graph illustrates the percentage of the world population within a geographic region (blue bars, The World Factbook July 2021 estimate; https://www.cia.gov/the-world-factbook/) and the percentage of gene therapy trials within each region (orange bars, ClinicalTrials.gov, accessed November 23, 2021).

diseases remains to be determined, but active research is ongoing.[31–34] We must also recognize that many of the coronavirus disease 2019 (COVID-19) vaccines were derived from gene therapy products developed for other indications.[35,36] Whether this technology could be leveraged for development of future therapies for other communicable diseases will have important implications for many LMICs.

CURRENT ACCESS TO GENE THERAPY

In 2021, there were at least 15 approved gene therapy products. Access to approved therapies remains very limited in LMICs and is almost exclusively through managed access and compassionate programs.[37] As of this writing, the only LMICs with approved gene therapy products are China, Brazil, and the Philippines.[38] Most individuals currently receiving gene therapy are enrolled in clinical trials using investigational agents. A survey of ClinicalTrials.gov on November 22, 2021, identified 171 recruiting trials (search term "gene therapy"). A significant number of trials are open in multiple sites and various countries. HICs support more trials, often with multiple open sites, favoring access to HIC participants (Table 1). Although there are a few trials open in upper middle-income countries, our search found no open trials in lower middle income and low-income countries. More evidence of existing disparity is seen when recruiting trials are considered relative to the population (Figure 1).

International perspectives

To address equitable access to gene and cell therapies, the ASGCT formed a Global Outreach Committee that held its inaugural meeting on January 30, 2020. Some of the first activities were half-day virtual symposia with investigators from LMICs. The goal was to exchange scientific information while learning about opportunities and challenges. The first three symposia highlighted some common themes and differing approaches to bringing therapies into the country. The seminars were recorded and are available for viewing through the ASGCT website (http://www.ASGCT.org).

Gene therapy in Brazil

On December 2, 2020, a joint initiative of the ASGCT Outreach Committee and the Brazilian Association of Cell and Gene Therapy (ABTCel) promoted a virtual forum with Brazilian and international researchers (https://asgct.org/brazil). The event described the experience of a Brazilian group during development, production, and clinical use of CAR-T cells. The discussion then turned to a planning plan for implementing clinical trials for single-gene diseases, covering the challenges and opportunities.

Brazil is a large country of continental dimensions and very diverse culturally, economically, and in terms of access to health care. The 1988 national constitution established the Unified Health System (SUS) as a universal right to face this challenging system. The country has a robust private health system that serves over a quarter of the population. The development of high-cost drugs and health inflation has challenged the sustainability of this model.[1] Currently, commercialization of a new drug requires National Health Surveillance Agency (ANVISA) approval. Incorporation into the public health system requires permission of the National Commission for the Incorporation of Technology in the SUS (CONITEC), an independent entity that follows principles of health economy and cost/effectiveness. As a result, there is a significant disparity in access to diagnosis, drugs, and procedures between the public and private systems, with oncology a paradigm for this challenge.

Anticipating the potential of advanced therapy medicinal products (ATMP) like gene and cell therapies, Brazil invested in developing and implementing a dozen cellular therapy centers in the early 2000s. This effort generated excellence groups, especially using hematopoietic or mesenchymal stem cells for cardiac and neuronal diseases. This led to the first clinical trial developed in Brazil using a plasmid intended to improve myocardial perfusion[2]. Unfortunately, only a few therapy centers were developed, and center distribution is still geographically uneven. Later efforts, including national legislation for the use of embryonic stem cells in 2005, on research ethics and regulation of genetically modified organisms have moved the field forward. One milestone was the recent resolution covering the

Please cite this article in press as: Cornetta et al., Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.04.002

research, development, clinical application, and registration of ATMPs. ANVISA also promoted a network of experts for ATMPs, called RENETA (https://www.reneta.org.br), who support evaluation of products and generate educational content regarding legislation and the development process for ATMPs.

Most of the science funding in Brazil is provided by federal or local funding agencies. Despite the vertiginous drop in investment in science and technology in the country as of 2016, the federal government opened a financing cycle for ATMP development.[3,4] To date, supported projects include pre-clinical and clinical therapies for leukemias and lymphomas (CAR-T), viral reinfections (virus-specific T cells), and retinal, cardiovascular, neuronal, and monogenic diseases. Approaches have included use of cell therapies, gene therapies with viral (adeno-associated virus, retrovirus, lentivirus, and adenovirus), non-viral vectors (plasmids and transposons), and CRISPR-based gene editing protocols.

Brazil is also leveraging centuries-old institutions renowned for developing health solutions, such as the Osvaldo Cruz Foundation and the Butantan Institute. Both institutions have produced or prepared most of the vaccines used against COVID-19 in Brazil. Initiatives are underway to leverage these institutions to boost manufacture of ATMPs. New centers for cell and gene therapy manufacturing are also being built, with additional capacity expected within the next 5 years.

Today, locally developed CAR-T cell therapy has been used to treat individuals with B cell lymphoma in a compassionate use protocol. As of March 2022, three commercially approved products (Zolgensma, Luxturna, and Kymriah) and 7 other industry-funded gene or cell therapies are in clinical trials. Treatment targets are hemophilia A and B, mucopolysaccharidosis type II, and leukemia, along with cellular therapies for leukemia and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

As the initiatives to use ATMPs in Brazil multiply (now largely driven by CAR-T trials), efforts and actions for the education and training of professionals, from development to translation, clinical use, and regulatory compliance, are urgent. A major challenge is to empower the ATMP research and development community to sustain the recent strong growth in this sector. To this end, rich discussions occurred in scientific forums, especially during events organized by local scientific societies and associations. The joint actions of local and international scientific entities are a promising way to strengthen ties and accelerate the development and implementation of ATMPs in Brazil.

Gene therapy in South Africa

On June 29, 2021, the ASGCT partnered with the South African Society of Haematology, the South African National Blood Service, The South African Society of Clinical Haematology, the South African Stem Cell Transplant Society, and the South African Bone Marrow registry for a half-day symposium. The presenters were a mix of local and international experts in monogenic diseases, cell therapy, and regulatory issues.

There are currently no approved gene therapy products in South Africa. Although the most significant challenge is cost, as summarized in a recent perspective,[39] additional issues are relevant. First, wealth distribution in South Africa is unequal, with a Gini index of 61 in 2021.[40]. Second, South Africa has a high disease burden of HIV, tuberculosis, malaria, and childhood treatable diseases. Therefore, moving resources from these entities to gene therapy is unlikely. Third, the current dual health system further deepens health inequality, with only 15% of the population using 80% of the health resources. A proposal for universal health coverage (UHC) is currently being piloted. This may allow individuals access to currently approved gene therapies if successfully implemented.

Research in gene and cell therapy is government-funded through the South African Medical Research Council (SAMRC). Funding is also available through competitive international grants (the Bill and Melinda Gates Foundation, the Global Fund, the National Institutes of Health, and the European Union). Finally, with the current COVID-19 pandemic, additional resources were made available, including from the World Health Organization, the African Centre for Disease Control, and many private partners. Although many of these funders are specifically funding vaccine efforts, there is no reason why the expertise and resources available could not be repurposed for gene therapy.

South Africa has a robust and globally aligned regulatory and research ethics framework to facilitate review and monitoring of gene therapy research.[41,42] Approval is needed from the South African National Department of Health (NdoH) for cell and gene therapies. In addition, gene therapy trials need approval from the Department of Fisheries and Forestry (DAFF), which oversees genetic modifications of plants, animals, and humans.

Although South African legislation provides for registration of new drugs through the South African Health Products Regulatory Authority (SAHPRA), there is currently no commercial gene therapy manufacturing pathway. To address this gap, Hendricks et al. have undertaken to detail the requirements for a national legislative plan for cell and gene therapy.[39] To advance basic science research, an infrastructure for gene therapy innovation has been established, initially focused on hepatitis B and then expanded to include hemophilia and COVID-19 mRNA vaccines.[43–46] In addition, Hendricks et al. are developing mesenchymal stromal stem cell therapies for both solid tumors and hematologic malignancies.[39]

Although there are presently no homegrown gene therapy clinical trials in South Africa, Mahlangu has set up a facility to conduct hemophilia gene therapy clinical trials and currently participates in several ongoing global hemophilia clinical trials.[47] Given the infrastructure costs and scarcity of expertise, South Africa has adopted the

Please cite this article in press as: Cornetta et al., Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.04.002

hub-and-spoke model, with hemophilia treatment centers referring to a single center for gene therapy infusions.

When cell and gene therapy products are commercially available, they will need to be evaluated and registered with the regulatory authority, SAHPRA. Affected individuals and their caregivers can access products not commercially available via section 21 of the National Health Act of South Africa. The regulatory authority who oversees this access pathway is required to review the application for risks and benefits and monitors individuals after treatment.

The key insights from the ASGCT-sponsored symposium included the need for collaboration and partnerships to bring similar educational webinars to the rest of Africa. It was clear from this online meeting that the ASGCT, with its global partners in all continents, is the correct entity to convene a meeting of this nature. The consequence of collaboration is capacity building to allow local scientists and clinicians to undertake accredited manufacturing and administration of gene therapy products and address the current unmet needs in cell and gene therapy.

Gene therapy in India

To promote and create awareness of gene and cell therapy, the virtual ASGCT Indo-UK Symposium on Clinical Gene Therapy was held on October 9, 2021. The goal was to bring multiple stakeholders together for a discussion of the status of gene and cell therapy in India. Advocacy groups for affected individuals were seen as key participants, along with clinicians, scientists, researchers, and industry representatives from India and the United Kingdom. Meeting co-sponsors included the CureSMA Foundation of India, the Organization for Rare Diseases India, Somaiya Ayurvihar, the Hemophilia Society Mumbai Chapter, the Indian Society for Clinical Research, and Spark Therapeutics. Topics were selected for their clinical importance and potential for implementation in the near future. They included gene therapy development in Leber congenital amaurosis, hemophilia, and CAR-T cell therapy for leukemia and lymphomas. Speakers from the Indian Council of Medical Research (ICMR) and the government agency NitiAayog were included in the symposium to provide an overview of the regulatory preparedness for rolling out clinical trials and the support mechanisms available from the government, respectively.

A special goal of the symposium was development of indigenous gene therapy technologies. Currently, CAR-T cell therapy has been approved for academic trials at the Advanced Centre for Treatment, Research, and Education at the Cancer/Indian Institute of Technology in Bombay and the Christian Medical College in Vellore. Although currently there are no commercial gene therapy clinical trials in the country, there will be indigenous trials starting in the latter part of 2022. Many other gene therapy trials are under consideration for approval. In a country like India, where conventional rare diseases are not "rare" and with a large population to serve, the government intends to drive self-reliance or "Atma Nirbhar." This is the only way the treatment can reach the population at large. To this end, India is investing resources to become a cost-effective manufacturing hub for gene and cell therapy products. In anticipation, multiple preclinical studies using viral vectors for treating hemophilia, Leber congenital amaurosis, thalassemia, and other diseases have been supported by the Department of Biotechnology (DBT) and the Wellcome Trust-DBT India Alliance. In addition, CAR-T cell trials within academic centers are currently supported by the ICMR, which has established a task force for gene therapy that is fueling work in several research areas.

The ICMR and DBT have developed the National Guidelines for Gene Therapy Product Development and Clinical Trials to facilitate gene therapy trials in India.[48] In addition, a Gene Therapy Advisory and Evaluation Committee (GTAEC) anchored at the ICMR has enlisted a diverse array of biomedical research experts and government agencies, the DBT, the Directorate General of Health Services, the Central Drugs Standard Control Organization, the Department of Science and Technology, the Medical Council of India, and other stakeholders. Among its diverse role, the GTAEC will also help guide potential stakeholders and provide advice to facilitate clinical trial submission for review. Final approval for a commercial product launch will be the purview of the Central Drugs Standard Control Organization and the Drug Controller General, India.

To help foster continued growth in gene therapy development, the ASGCT-sponsored symposium made a special effort to advertise the meeting to young professionals in medical colleges throughout India. Going forward, the organizers encourage the ASGCT to function as matchmakers between society members and those working in India, developing novel clinical trials, vector production facilities, and increasing cell manufacturing capacity. The ASGCT is also encouraged to promote twinning programs to fast-track development and foster opportunities for collaboration.

Industry perspectives

The ASGCT Global Outreach conference discussions indicated the critical role of the industry in global access. From an industry perspective, there are technical and logistic hurdles for this class of therapeutic agents. Data on long-term issues related to integrational mutagenesis, immunogenicity, and persistence of therapeutic effect are still accruing. Manufacturing of cell and gene therapies remains costly and technically challenging, requiring significant upfront investment in product development, and contributes to the high cost of this class of therapeutic agents. Although these obstacles are not unsurmountable, more work is needed to increase manufacturing capacity and decrease costs when gene therapy becomes a mainstream therapeutic modality.

Given that genetic diseases represent the majority of gene-based therapies with reliable preclinical data, patient identification and enrollment in clinical trials remain crucially important for the success of the field. Although the number is still limited, LMICs have been considered for late-phase clinical trials, when larger populations of affected individuals are being enrolled in well-defined clinical

Please cite this article in press as: Cornetta et al., Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.04.002

protocols. There are typically preliminary safety and efficacy profiles regarding the agent being investigated in these studies. To date, the involvement of LMICs in early-phase trials has been limited because these trials typically enroll a relatively small cohort of participants. Consistency and control over supportive care are critical when assessing safety and reaching meaningful conclusions. Standardizing supportive care in a single HIC can be challenging, and conducting trials internationally presents an even greater challenge. The availability of centers of excellence capable of characterized gene mutations, providing access to cohort of affected individuals, and administering advanced therapeutic agents in the context of controlled trials would certainly attract the interest of small and large developers of cell and gene therapy products by addressing these concerns.

As noted by participants at the ASGCT Global Outreach Symposia, the availability of the right framework for timely regulatory review and approval for clinical trials is of concern for academic gene therapy researchers, and this challenge is shared by those in the industry seeking to provide commercial products. Ethical considerations are also crucially important in the context of gene and cell therapies. Compounding the unique regulatory landscape in an individual country, industry must also assess the legal framework governing liability and intellectual property protections. Addressing these limitations by providing clear guidelines for regulatory approval and a solid legal framework can improve access to gene and cell therapy trials, whether the country is an HIC or LMIC.

The high cost of this class of therapeutic agents remains a major limitation of access, and this is particularly true in LMICs. Innovative reimbursement models, such as installments over time and rebates, have been discussed as potential ways to facilitate the commercialization of gene therapy drugs in developed economies. For LMICs, access to approved gene therapies is limited chiefly to compassionate and managed access programs, which are not reaching all eligible individuals. As technological advances decrease the cost of manufacturing, future efforts will be required to explore better solutions for access in LMICs.

CONCLUSIONS

Many of the gene therapy products being developed in HICs address diseases with a high prevalence in LMICs. The three participants in the ASGCT-sponsored symposia confirmed government support of gene therapy research and a desire to participate in clinical trials. Two of the countries are developing infrastructure to manufacture gene and cell therapy products, and all are developing specialized clinical care centers. A major driver for developing in-country resources is the anticipated cost of commercial products.

The ASGCT symposia were held with upper middle-income countries, and many lower-income countries may not have the resources to invest in gene therapy at this time. In regions where the health infrastructure is limited, developing cancer and newborn screening will have a broader effect on population health. As more health services are developed, there may be situations where early implementation of gene therapy may be advantageous. For example, in countries where individuals lack access to hemophilia treatment, onboarding a curative gene therapy may be advantageous compared with developing infusion centers and the cost of life-long factor replacement.[49] Although many in HICs, including the ASGCT, are discussing access to gene therapy, it is important for each country to decide how and when to make gene therapies available. Each country is best able to balance healthcare priorities, financial resources, and available infrastructure.

Gene therapies are inherently expensive to produce, and companies and academic institutions are working to decrease the manufacturing costs. More challenging is the price pharmaceutical companies affix to novel therapies, which warrants development of innovative payment models, as an example of a potential solution for the issue. The ethics and solutions for this issue continue to be debated and are beyond the scope of this manuscript. There is a lesson from the HIV epidemic to consider as gene therapies are shown to be safe and effective. When anti-retroviral drugs (ARVs) became available in HICs, there were those who argued that access to these drugs was not feasible in LMICs and that efforts should focus on prevention.[50] As HIV incidence and deaths climbed, advocacy groups successfully pushed governments, pharmaceutical companies, and international aid organizations to provide access to care.[51] A similar coalition will likely be needed to bring a gene therapy product into some LMIC health systems.

Our symposium feedback encouraged continued educational efforts by the ASGCT. Specifically, efforts aimed at scientists and clinicians will be important to foster development of clinical trials and treatments. To this end, the ASGCT will hold a follow-up forum with Brazilian investigators, and a symposium with investigators in the Middle East is planned for June 2022. The ASGCT also hopes to develop a Train the Trainers program in collaboration with an LMIC university. The goal is to provide a certificate course to empower faculty at LMIC universities and medical schools to add gene therapy to their curriculum. The symposium feedback also confirmed an educational need regarding regulatory review and approval of gene therapy. The ASGCT is currently discussing virtual training to assist with meeting this educational need.

Gene therapy holds promise for many life-limiting diseases in LMICs. Just as improvements in efficacy, safety, and cost for gene therapies requires investment, so do efforts to foster communication, education, and collaboration if we are to improve global access to these novel therapies.

ACKNOWLEDGMENTS

K.C. was supported by the Fulbright Scholar Program during writing of this manuscript and is funded by the National Heart, Lung and Blood Institute (contract 75N92019D00018 and 1R41HL155004). Indiana University has licensed technology from the Cornetta laboratory to Charles River Laboratories. M.B. is supported by CNPq (National Council for Scientific and Technological Development) (grants

Please cite this article in press as: Cornetta et al., Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.04.002

313106/2020-7 and 311761/2018-6), FAPERJ (Foundation for Research Support of the State of Rio de Janeiro) (grant CNE-E-26/202.645/2019). F.M. is an employee of Spark Therapeutics, a Roche company, and an equity holder in Roche.

AUTHOR CONTRIBUTIONS

K.C., M.B., J.M., F.M., S.R., and J.R. participated in conceptualization, writing of the original draft, and review and editing of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Rosenberg, S.A., Aebersold, P.M., Cornetta, K., Kasid, A., Morgan, R.A., Moen, R., Karson, E.M., Lotze, M.T., Yang, J.C., Topalian, S.L., et al. (1990). Gene transfer into humans-immunotherapy of patients with advanced melanoma, using tumor infiltrating lymphocytes modified by retroviral gene transduction. N. Engl. J. Med. *323*, 570–578.
2. MIT NEWSDIGS Research Brief (2020). Updated Projection of US Durable Cell and Gene Therapies Product-Indication Approvals Based on December 2019 Development Pipeline (Massachusetts Institute of Technology, FoCUS).
3. Yla-Herttuala, S. (2015). Glybera's second act: the curtain rises on the high cost of therapy. Mol. Ther. *23*, 217–218.
4. Senior, M. (2017). After Glybera's withdrawal, what's next for gene therapy? Nat. Biotechnol. *35*, 491–492.
5. Kolata, G. (2017). New Gene-Therapy Treatments Will Carry Whopping Price Tags (New York Times).
6. National Public Radio (2019). At $2.1 Million, New Gene Therapy Is the Most Expensive Drug Ever.
7. Howson, C.P., Cedergren, B., Giugliani, R., Huhtinen, P., Padilla, C.D., Palubiak, C.S., Santos, M.D., Schwartz, I.V.D., Therrell, B.L., Umemoto, A., Wang, J., et al. (2018). Universal newborn screening: a roadmap for action. Mol. Genet. Metab. *124*, 177–183.
8. Therrell, B.L., Jr., and Padilla, C.D. (2018). Newborn screening in the developing countries. Curr. Opin. Pediatr. *30*, 734–739.
9. Yadav, H., Shah, D., Sayed, S., Horton, S., and Schroeder, L.F. (2021). Availability of essential diagnostics in ten low-income and middle-income countries: results from national health facility surveys. Lancet Glob. Health *9*, e1553–e1560.
10. World Health Organization. (2011). Increasing Access to Diagnostics through Technology Transfer and Local Production. https://www.who.int/phi/publications/Increasing_Access_to_Diagnostics_Through_Technology_Transfer.pdf.
11. Espina, C., McKenzie, F., and Dos-Santos-Silva, I. (2017). Delayed presentation and diagnosis of breast cancer in African women: a systematic review. Ann. Epidemiol. *27*, 659–671.e7.
12. Pierz, A.J., Randall, T.C., Castle, P.E., Adedimeji, A., Ingabire, C., Kubwimana, G., Uwinkindi, F., Hagenimana, M., Businge, L., Musabyimana, F., et al. (2020). A scoping review: facilitators and barriers of cervical cancer screening and early diagnosis of breast cancer in Sub-Saharan African health settings. Gynecol. Oncol. Rep. *33*, 100605.
13. Ginn, S.L., Amaya, A.K., Alexander, I.E., Edelstein, M., and Abedi, M.R. (2018). Gene therapy clinical trials worldwide to 2017: an update. J. Gene Med. *20*, e3015.
14. Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., and Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. *71*, 209–249.
15. McKenzie, F., Zietsman, A., Galukande, M., Anele, A., Adisa, C., Parham, G., Pinder, L., Cubasch, H., Joffe, M., Kidaaga, F., Lukande, R., et al. (2018). Drivers of advanced stage at breast cancer diagnosis in the multicountry African breast cancer - disparities in outcomes (ABC-DO) study. Int. J. Cancer *142*, 1568–1579.
16. Grover, S., Martei, Y.M., Puri, P., Prabhakar, P., Mutebi, M., Balogun, O.D., Price, A.J., Freeman, A.H., Narasimhamurthy, M., Rodin, D., et al. (2018). Breast cancer and HIV in sub-saharan Africa: a complex relationship. J. Glob. Oncol. *4*, 1–11.
17. Allemani, C., Weir, H.K., Carreira, H., Harewood, R., Spika, D., Wang, X.S., Bannon, F., Ahn, J.V., Johnson, C.J., Bonaventure, A., Marcos-Gragera, R., et al. (2015). Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet *385*, 977–1010.
18. Baird, P.A., Anderson, T.W., Newcombe, H.B., and Lowry, R.B. (1988). Genetic disorders in children and young adults: a population study. Am. J. Hum. Genet. *42*, 677–693.
19. Jayasundara, K., Hollis, A., Krahn, M., Mamdani, M., Hoch, J.S., and Grootendorst, P. (2019). Estimating the clinical cost of drug development for orphan versus non-orphan drugs. Orphanet J. Rare Dis. *14*, 12.
20. Piel, F.B., Steinberg, M.H., and Rees, D.C. (2017). Sickle cell disease. N. Engl. J. Med. *376*, 1561–1573.
21. Piel, F.B., Patil, A.P., Howes, R.E., Nyangiri, O.A., Gething, P.W., Dewi, M., Temperley, W.H., Williams, T.N., Weatherall, D.J., and Hay, S.I. (2013). Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet *381*, 142–151.
22. Novartis, A.G. (2021). Global Impact of SCD. https://www.notaloneinsicklecell.com/Global-Impact-Of-SCD/#s21.
23. Esrick, E.B., Lehmann, L.E., Biffi, A., Achebe, M., Brendel, C., Ciuculescu, M.F., Daley, H., MacKinnon, B., Morris, E., Federico, A., Abriss, D., et al. (2021). Post-transcriptional genetic silencing of BCL11A to treat sickle cell disease. N. Engl. J. Med. *384*, 205–215.
24. Ribeil, J.A., Hacein-Bey-Abina, S., Payen, E., Magnani, A., Semeraro, M., Magrin, E., Caccavelli, L., Neven, B., Bourget, P., El Nemer, W., Bartolucci, P., et al. (2017). Gene therapy in a patient with sickle cell disease. N. Engl. J. Med. *376*, 848–855.
25. Winter, L. (2021). Gene Therapy for SIckle Cell Not Linked to Cancer, Bluebird Finds. https://www.the-scientist.com/news-opinion/gene-therapy-for-sickle-cell-not-linked-to-cancer-study-68540.
26. Frangoul, H., Ho, T.W., and Corbacioglu, S. (2021). CRISPR-Cas9 gene editing for sickle cell disease and beta-thalassemia. Reply. N. Engl. J. Med. *384*, e91.
27. World Federation of Hemophilia. (2021). Report on the Annual Global Survey 2020. https://www1.wfh.org/publications/files/pdf-2045.pdf.
28. Pierce, G.F., Coffin, D., and Members of the, W.F.H.G.T.R.T.P.C., Organizing, C.. (2019). The 1st WFH Gene Therapy Round Table: understanding the landscape and challenges of gene therapy for haemophilia around the world. Haemophilia *25*, 189–194.
29. US Central Intellegence Agency (2020). HIV/AIDS - adult prevalence rate. In The World Factbook, https://www.cia.gov/the-world-factbook/field/hiv-aids-adult-prevalence-rate/country-comparison.
30. UNICEF (2021). Under-five Mortality. https://data.unicef.org/topic/child-survival/under-five-mortality/.
31. Rogers, G.L., and Cannon, P.M. (2017). Gene therapy approaches to human Immunodeficiency virus and other infectious diseases. Hematol. Oncol. Clin. North Am. *31*, 883–895.
32. Yusuf, Y., Yoshii, T., Iyori, M., Yoshida, K., Mizukami, H., Fukumoto, S., et al. (2019). Adeno-associated virus as an effective malaria booster vaccine following adenovirus priming. Front. Immunol. *10*, 730.
33. Ahlenstiel, C.L., and Turville, S.G. (2019). Delivery of gene therapy to resting immune cells for an HIV cure. Curr. Opin. HIV AIDS *14*, 129–136.
34. Giri, B.R., Mahato, R.I., and Cheng, G. (2019). Roles of microRNAs in T cell immunity: implications for strategy development against infectious diseases. Med. Res. Rev. *39*, 706–732.
35. Nakagami, H. (2021). Development of COVID-19 vaccines utilizing gene therapy technology. Int. Immunol. *33*, 521–527.
36. Vandenberghe, L.H. (2020). COVID-19: gene transfer to the rescue? Hum. Gene Ther. *31*, 605–607.

Please cite this article in press as: Cornetta et al., Gene therapy access: Global challenges, opportunities, and views from Brazil, South Africa, and India, Molecular Therapy (2022), https://doi.org/10.1016/j.ymthe.2022.04.002

37. Novartis. (2021). Novartis Gene Therapies Recommits to Global Managed Access Program for 2021. https://www.novartis.com/news/novartis-gene-therapies-recommits-global-managed-access-program-2021.

38. Exothera. (2021). Viral Vectored Gene Therapies Approved at a Glance. https://exothera.world/worldwide-approved-gene-therapies-based-on-viral-vectors/.

39. Hendricks, C.L., Alessandrini, M., and Pepper, M.S. (2022). Equitable access to cell and gene therapies in South Africa: opportunities and hurdles. Gene Ther. https://doi.org/10.1038/s41434-021-00309-y.

40. World Population Review (2020). Gini Coefficient by Country. https://worldpopulationreview.com/country-rankings/gini-coefficient-by-country.

41. Department of Health, Republic of South Africa (2020). South African Good Clinical Practice: Clinical Trial Guidelines. https://www.sahpra.org.za/wp-content/uploads/2021/06/SA-GCP-2020_Final.pdf.

42. Department of Health, Republic of South Africa (2015). Ethics in Health Research: Principles, Processes and Structures. https://www.sun.ac.za/english/research-innovation/Research-Development/Documents/Integrity%20and%20Ethics/DoH%202015%20Ethics%20in%20Health%20Research%20-%20Principles,%20Processes%20and%20Structures%202nd%20Ed.pdf.

43. Arbuthnot, P., Maepa, M.B., Ely, A., and Pepper, M.S. (2017). The state of gene therapy research in Africa, its significance and implications for the future. Gene Ther. *24*, 581–589.

44. (2017). Antiviral Gene Therapy Research Unit - Wits University. https://www.wits.ac.za/agtru/.

45. Ely, A., Bloom, K., Maepa, M.B., Mahlangu, J.N., Pepper, M.S., and Arbuthnot, P. (2019). Gene and cell therapy in South Africa: current status and future prospects. S Afr. Med. J. *109*, 12–16.

46. (2019). South Africa COVID 19 mRNA Vaccine Hub. https://www.samrc.ac.za/mediarelease/south-africa-establishes-world-class-consortium-create-first-technology transfer-hub.

47. Mahlangu, J.N. (2020). Requirements to participate in haemophilia clinical trials. Haemophilia *26*, 22–25.

48. Indian Council of Medical Research (2019). National Guidelines for Gene Therapy Product Development and Clinical Trials (Research ICoM, Ed.) (Indian Council of Medical Research), https://main.icmr.nic.in/sites/default/files/guidelines/guidelines_GTP.pdf.

49. Mahlangu, J., Cerquiera, M., and Srivastava, A. (2018). Emerging therapies for haemophilia - global perspective. Haemophilia *24*, 15–21.

50. Cochrane, J. (2000). Narrowing the gap: access to HIV treatments in developing countries. A pharmaceutical company's perspective. J. Med. Ethics *26*, 47–50, discussion 51-43.

51. Darder, M., McGregor, L., and Devine, C. (2014). No Valley without Shadows. MSF and the Fight for Affordable ARVs in South Africa, Médecins Sans Frontières/Doctors without Borders: Rue Dupré 94, 1090. https://www.msf.org.za/news-and-resources/publications/no-valley-without-shadows.