A FRAMEWORK TO STRENGTHEN HEALTH SYSTEMS FOR GENE THERAPY FOR RARE GENETIC DISEASES

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EXECUTIVE SUMMARY

With advancements in technology and science, we are at the cusp of scientific innovation with exciting new genetic medicines on the horizon. The scientific community has made incredible advances in the development of new innovative therapies, such as gene therapies, which the FDA predicts 10–20 new licensed cell and gene therapy medicines annually by 2025 in the United States alone. Gene therapy is a new treatment paradigm that reaches beyond traditional disease management and targets the root cause of a disease with the goal to stop or slow its progression. This approach has the potential to be transformative, changing the course of a disease and reducing the long-term patient and health system burdens associated with chronic disease management. While gene therapy represents a radical shift in our approach to disease treatment, this novel approach poses new challenges for health systems that we must address in order to ensure patients can benefit from these innovations once approved.

In October 2022, Pfizer and the Alliance for Regenerative Medicine convened a roundtable at the World Health Summit bringing together representatives across stakeholders—including academia, civil society, industry, patient communities, healthcare professionals, and governments—to learn about advances in gene therapy and discuss current health system barriers and potential solutions to gene therapy delivery and access.

The roundtable provided an initial forum for examining barriers and potential opportunities to strengthen care delivery and patient access to approved gene therapies. The roundtable focused on two specific areas where governments and health systems can take action—care delivery and patient access.

CARE DELIVERY FOR GENE THERAPY:

BARRIERS	OPPORTUNITIES
Lack of infrastructure for diagnosis and determining patient eligibility for gene therapy	• Support Multi-Stakeholder Education • Strengthen Infrastructure for Newborn Screening (NBS) • Develop Governance Frameworks for Eligibility and Referrals
Lack of infrastructure for gene therapy delivery	• Certify National Centers of Excellence (COEs) • Integrate Hub-and-Spoke Model • Connect COEs across Countries

ACCESS TO GENE THERAPY

BARRIERS	OPPORTUNITIES
Challenges for the appropriate value assessment for gene therapies	• Engage in Early Dialogue • Review Value Assessment Methodologies to Ensure Processes are Fit for Gene Therapies • Support Multi-Stakeholder Models of Advanced Therapy Medicinal Product (ATMP) Development
Challenges for the adoption of innovative financing models	• Support Horizon Scanning and Education • Support the Use of Novel Payment Models

While there are many known barriers and opportunities, this *Framework* focuses on a select few that were discussed during the roundtable dialogue and have a relatively high impact on preparedness for gene therapy for rare diseases. This *Framework* aims to serve as a starting point for conversations around barriers and opportunities for gene therapy delivery and access.

To surmount the various complex health system barriers, countries can implement the potential opportunities offered in this *Framework* at the level and scale appropriate for their current levels of readiness and health system priorities. Patients will be the ultimate and most important beneficiaries of such efforts, and they also need to be included as co-leaders and co-creators.

THE PROMISE AND POTENTIAL OF GENE THERAPY

Gene therapies have the potential to transform the lives of people living with devastating rare diseases. There are an estimated 300+ million people living with a rare disease around the world, of which more than 80% are genetic in origin.[1] Many of these genetic rare diseases have degenerative, irreversible, and devastating disease progression which places a heavy burden on individuals, families, and care providers.[2]

Traditional approaches to rare disease management are often limited to symptom management, with few able to address the underlying genetic cause.[3] The emerging technology of gene therapy presents a new treatment paradigm with the aim of being able to fully or partially restore protein function, allowing for therapies with mechanisms of action that directly target the root cause of disease.[4] This has the potential to be transformative for many rare disorders, slowing or stopping progression and ultimately changing the course of disease, which can have profound impact on individuals living with rare diseases and reducing the burden and long-term costs associated with current disease management. The approval of safe, efficacious gene therapies is a highly anticipated step forward for science and patients.[5]

The promise of gene therapies is now becoming a reality, with the US FDA predicting 10–20 new licensed cell and gene therapy medicines annually by 2025 in the United States alone.[6,7] While gene therapies represent a radical shift in the potential for improving outcomes for people with rare diseases, their implementation also poses substantial and unique challenges for health systems. These challenges are wide ranging, spanning from diagnosis and determining eligibility, ensuring infrastructure and processes are in place for proper monitoring and follow-up, and access through payer systems. Given the complexity of the changes required, and the number of therapies that will soon be licensed, there is a need to act now to ensure that health systems are ready to embrace the potential of gene therapies.

The Potential Impact of Gene Therapy

Potential for one-time treatment of rare diseases

Eliminate need for ongoing therapies, or the burden of daily disease management

Reduce – or eliminate – costs associated with years of chronic care management over a patient's lifetime, lessening the long-term economic burden of disease

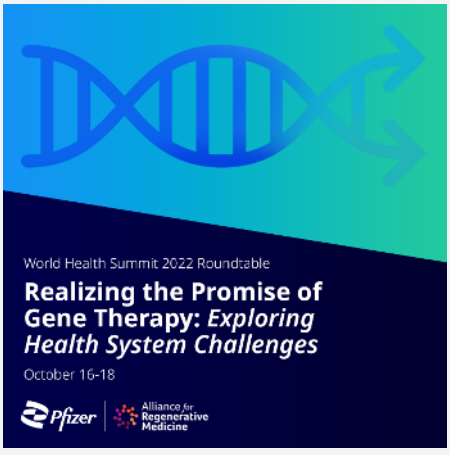
Enable patients to live longer, healthier, and more productive lives, increasing their contribution to their communities and the overall economy

**Note: If successful, investigative strategies to reduce the effect of anti-AAV neutralizing antibodies may increase gene-therapy options for patients with pre-existing antibodies and potentially enable redosing in the future.*

GENE THERAPY ROUNDTABLE DISCUSSION AT THE 2022 WORLD HEALTH SUMMIT

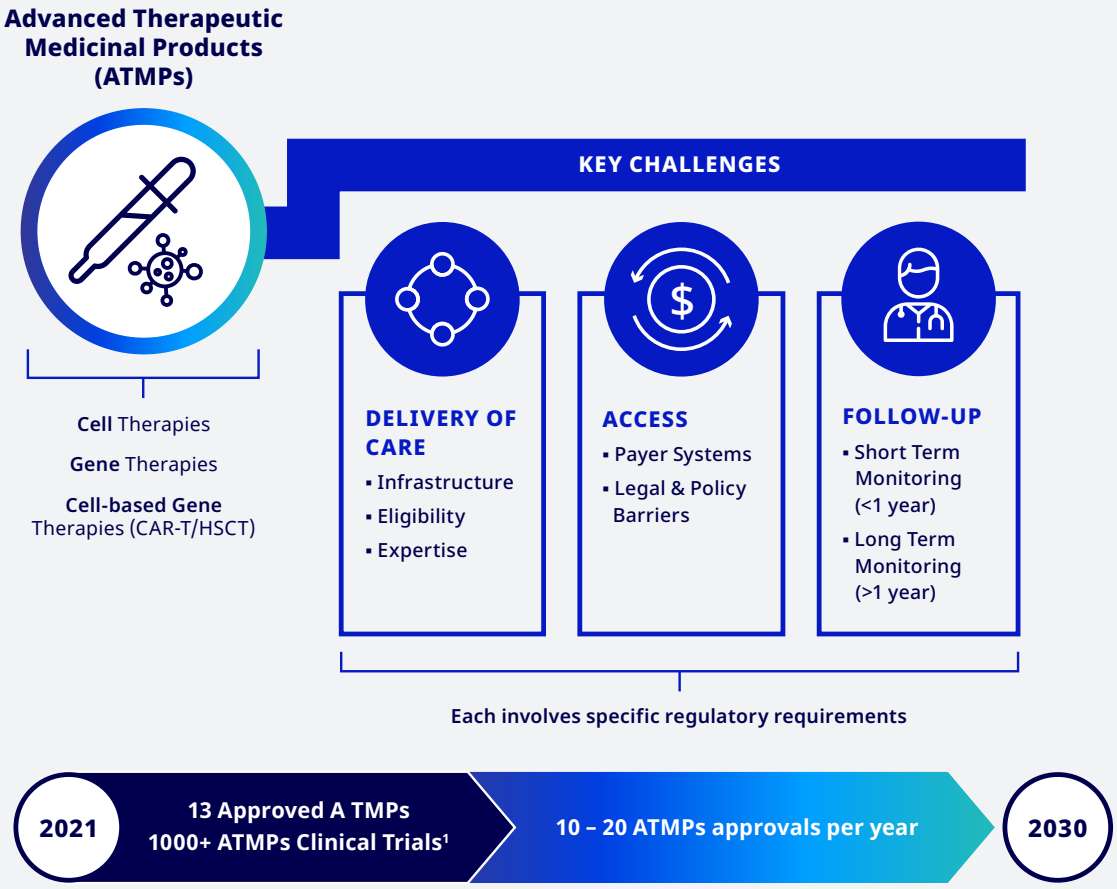
During the World Health Summit in Berlin, Germany, the Alliance for Regenerative Medicine (ARM) and Pfizer co-hosted a roundtable on 17 October 2022. The roundtable convened a group of multi-sector stakeholders, including government officials, academic experts, medical societies, healthcare professionals (HCPs), patient organization representatives, and industry leaders to discuss how countries across diverse geographies and health systems could facilitate access to gene therapies. Participants shared strategies and recommendations for strengthening health systems to ensure they are prepared to bring these new innovative therapies to patient populations. Participants recognized that there is no one-size-fits-all approach, acknowledging significant differences between high-income countries (HICs) and low- and middle-income countries (LMICs) in available health system resources. The roundtable culminated in the development of a report titled, *Framework to Strengthen Health Systems for Gene Therapy for Rare Genetic Diseases*, intended to provide recommendations for key health system stakeholders—including but not limited to health policymakers and other government officials—on a plan of action for facilitating delivery and access to approved, forthcoming gene therapies.

Participants of the roundtable included representatives from: Pfizer, Alliance for Regenerative Medicine (ARM), American Society of Gene & Cell Therapy (ASGCT), Canadian Organization for Rare Disease (CORD), European Hemophilia Consortium, EURORDIS – Rare Diseases Europe, Foundation Council of the Swiss Institute of Bioinformatics, Irish Hemophilia Society, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Karolinska Institute, King Faisal Specialist Hospital & Research Centre, Faster Cures – Milken Institute, Ministry of Health – Brazil, Parent Project Muscular Dystrophy, Paul-Ehrlich-Institut – German Federal Institute for Vaccines and Biomedicines, Project VITA, Rare Diseases International (RDI), Spanish Federation of Rare Diseases (FEDER), Ibero-American Rare Diseases Alliance (ALIBER), Università Cattolica del Sacro Cuore, Faculty of Economics, University of Freiburg, Victorian Department of Health in Australia and the World Medical Association.



Structure of the Framework

The roundtable provided an initial forum for examining challenges and potential opportunities to strengthen care delivery and patient access to approved gene therapies. This *Framework* identifies "Health System Barriers" and "Health System Opportunities" in two areas: (1) Care Delivery and (2) Patient Access (see Figure 1). Health System Barriers are defined as bottlenecks, gaps, or challenges that hinder care delivery and access to gene therapy. Health System Opportunities are public policies, regulations, health system interventions or initiatives that could help facilitate care delivery and access to gene therapy. While there are many known barriers and opportunities, this *Framework* focuses on a select few that were discussed during the roundtable dialogue and have a relatively high impact on preparedness for gene therapy for rare diseases. This *Framework* aims to serve as a starting point for conversations around barriers and opportunities for gene therapy delivery and access.



HEALTH SYSTEM BARRIERS AND OPPORTUNITIES

Barrier 1: Lack of infrastructure for diagnosis and determining patient eligibility for gene therapy

People living with a rare disease typically face a complex and often arduous "diagnostic odyssey." This journey starts from the suspicion of a health condition based on family history, delayed development, and/or onset of symptoms and ends with achieving an accurate diagnosis of the disease. On average, this odyssey lasts 5 years or longer before arriving at the correct diagnosis, and could potentially have many incorrect diagnoses along the way.[8] This is partly due to the difficulty of diagnosing rare diseases: in some cases, patients, families, and even HCPs may not recognize the symptoms of a particular rare disease, especially if it affects very few people (often less than one in 1 million). Additionally, some rare diseases are heterogenous, meaning the symptoms may differ from person to person, which further complicates the diagnosis. The genetic cause of rare diseases can also be complex, with some rare genetic diseases caused by a single-gene mutation, while others may involve multiple genes.

Lack of awareness, expert knowledge, and access to the appropriate tests and/or specialists can lead to delayed care or misdiagnosis. For patients, this can mean unnecessary tests and procedures, additional hospital admissions, delays in care, and inappropriate disease management.[8] As a result, the patient may not receive timely and appropriate intervention, sometimes with serious or even fatal consequences.

As gene therapies become available, early accurate diagnosis could be life-changing in the first few months/years of life. In eligible patients, early administration of gene therapy can potentially prevent the onset of symptoms or delay disease progression, with the goal that patients could live symptom-free for the rest of their lives. In addition to patients and their families, health systems and society could also benefit from avoiding the long diagnostic odyssey, saving valuable financial, technical, and human resources which could be better invested elsewhere.

The most efficient and cost-effective strategy for early diagnosis is newborn screening (NBS).[9] With advancements in technology and science and a growing awareness of rare diseases, NBS programs are rapidly expanding worldwide in scope and scale. This growth in NBS programs is likely to continue in future years, driven by the emergence of innovative treatments, such as gene therapies and other targeted therapies. Many rare diseases have a small window of opportunity for intervention before the onset of symptoms, such as spinal muscular atrophy and severe combined immunodeficiency. Thus, early diagnosis before the first clinical manifestations can promote timely access to life-changing treatments for optimal health and social outcomes, effectiveness, and value. However, even where the value of NBS is recognized, there may not be sufficient diagnostic equipment and trained personnel to carry out the screening. Greater investment in infrastructure and increased urgency among key political stakeholders are needed to ensure wider implementation of NBS.

Beyond diagnosis, treatment availability depends on many factors and careful consideration of whether gene therapy is appropriate for a particular patient is essential. Eligibility for gene therapies often depends on age, disease status, general health status, previous or current therapies, and other factors, such as neutralizing antibodies to the viral vector that transports the gene. Therefore, determining patient eligibility for gene therapy requires establishment of clear clinical practice recommendations, access to the correct diagnostic tools, and specially trained healthcare professionals.

When eligibility is confirmed, patients and their families must still make an informed decision as to whether they wish to proceed with administration of gene therapy. Sufficiently educating patients and families such that they can make an informed decision is no small task: the novel and highly technical nature of gene therapy makes it difficult for patients and families to understand, amidst a backdrop of lack of public trust and political support in the technology.

To overcome these barriers, comprehensive fact-based education needs to be designed to meet the needs of diverse stakeholder groups, including health professionals, policymakers, payers, caregivers and patients. The scope, scientific depth, and format of the education should be deliberately constructed with the insights of all stakeholders to ensure opportunities for engagement by all. Multi-stakeholder and multi-stage communication and education programs need to be provided on the basics around genetics, the different technologies, science, manufacturing, ethics, and clinical eligibility, to inform providers, patients, caregivers, and policymakers about the potential of gene therapy for rare genetic diseases.

Opportunities:

Support Multistakeholder Education:

- Comprehensive clinical workforce training related to gene therapy, including basics on genetics, science/technology, ethics, risks/benefits, and clinical eligibility, integrated into formal medical education curricula and available to HCPs after therapies are approved. Organizations such as the European Society for Gene & Cell Therapy (ESGCT) have developed a communication hub to support healthcare provider education.
- Educational communication, based in health literacy principles, to patients, caregivers, and policymakers on the technology, eligibility requirements, risks, benefits, and potential value of gene therapy. For example, to address the needs highlighted above, the EuroGCT project, funded by the EU Horizon 2020 program, is currently developing a communication hub to support HCPs, patients, and public education with reliable and accessible information.

Strengthen the Infrastructure for Newborn Screening (NBS):

- A nationally consistent, reimbursed newborn screening program.
- Government-level horizon scanning of gene & cell therapies in the clinical trial pipeline, focusing on the ones with a breakthrough designation at the FDA or a Prime designation at the EMA. A subsequent proactive pathway to support the inclusion of these rare diseases in NBS ahead of approval of relevant treatments.

Develop a Governance Framework for Eligibility and Referrals:

- A national health data governance framework and infrastructure to collect and secure patient data to facilitate diagnosis and eligibility determination, referral to facilities for administration and care, and short-term clinical monitoring for safety and efficacy.
- A government-hosted multi-stakeholder consortium to coordinate the location of and responsibility for care delivery for specific patients. For example, Australia is considering adopting a CAR-T care coordination model for gene therapy, under which state and territory governments support clinicians to convene a monthly multi-stakeholder patient board to determine eligibility and coordinate care referral plans for all potentially eligible gene therapy patients.

Barrier 2: Lack of infrastructure for gene therapy delivery

Patients may face an additional web of complex barriers when navigating the care delivery pathway before and during gene therapy administration, and during short-term and long-term follow-up.[10] Gene therapies are highly specialized, and their care pathway is complex, requiring a multidisciplinary care team, expertise, and technical capabilities. The care plan may require patients and families to remain near an administration site for some time. Moreover, specialized HCPs must work with a patient's primary HCP and care coordinators. With regards to gene therapies, there is regulatory variability across the globe, which requires an understanding of the regulatory requirements in each country or region. Due to the difference in global regulatory expectations, manufacturers may need to accommodate differences in registered details (e.g., process, specifications, and methods) for the same product across the globe.

Specialist clinics and centers supporting diagnosis, care, treatment, and research have been established for some rare diseases. These diseases include hemophilia, cystic fibrosis, multiple sclerosis, muscular dystrophy, Fabry Disease, and ALS.[11-16] For other rare conditions with smaller patient populations, less scientific understanding, lower profile, and fewer resources, centers of excellence (COEs) that encompass multiple rare diseases facilitate the diagnosis, care, and treatment of patients with ultra-rare conditions. The COEs also play a critical role in generating medical and scientific knowledge. University hospitals across several countries—including Australia, Canada, Finland, Israel, Italy, Japan, the Netherlands, Singapore, Sweden, and the United States—host centralized multi-disease COEs that support the coordination of care, sharing of best practices, resources, and research and training collaboration.[17]

In addition to centralized, stand-alone COEs, a hub-and-spoke model of care may also prove effective. In this model, COEs are connected to a network of smaller, geographically dispersed facilities to help ensure safe and effective administration, follow-up, and care delivery across large populations and geographic areas.[18] An advantage of this model is that it may overcome competition between local facilities and COEs, where, in certain countries, COEs may be incentivized to keep patients under their care rather than collaborating with other facilities. Competitive pressures could be further reduced by giving COEs and community-level facilities specific and equally critical roles related to gene therapy care delivery, administration, and follow-up. For example, community facilities could help reduce

travel and cost burden on patients by providing them with local care and conducting long-term follow-up, allowing COEs to focus their resources on gene therapy administration, short-term follow-up, and monitoring for potential early adverse events.

By creating a smarter allocation of resources across facilities, the hub-and-spoke model is a promising proposal that can facilitate access but would require additional time and effort to establish in any given country. As such, a pilot or phased approach to developing and scaling a robust national, provincial/state, or international care delivery pathway for gene therapy of rare genetic diseases will likely be necessary. Such a pilot could focus on a single therapeutic indication or therapeutic area and incorporate learnings from other specialty care models. In addition to appropriate care facilities, countries will need to implement policy frameworks to standardize models of care in COEs and hub-and-spoke facilities when ready to scale.

The transformational potential of gene therapies is also dependent on complex manufacturing infrastructure and processes. Furthermore, administration facilities need a fit-for-purpose system of processes, infrastructure, and equipment for adequately ordering, tracking, storing, and handling therapies. One distinct challenge in the gene therapy manufacturing space is limited globally-harmonized expectations and standards. Once a product is manufactured, its unique needs include cold chain distribution and storage requirements. Accordingly, insufficient infrastructure for gene therapy manufacturing, administration, and delivery of care is expected to be a critical barrier to patients accessing gene therapy.

Opportunities:

Certify National Centers of Excellence (COEs):

- Identify processes and/or legislative frameworks for independent assessment and accreditation/certification of centers of excellence.
- Nationally endorsed gene therapy centers of excellence across therapeutic areas that can facilitate diagnosis, determine eligibility, and deliver care. The Rare Impact Project has developed a proposal for a core set of quality and technical criteria for selecting and approving treatment centers that deliver gene therapies to generate alignment across varying stakeholder requirements.

Integrate Hub-and-Spoke Model:

- Pilot (single indication or therapeutic area) hub-and-spoke model of care, in which COEs are connected to a network of smaller, geographically dispersed facilities.
- Formally integrate community facilities into the care delivery process through the hub-and-spoke care delivery model to ensure community and rural centers are included.

Connect Centers of Excellence (COEs) across Countries:

- Facilitate and encourage COE participation in initiatives and reference networks to digitally connect expertise across countries that have limited expertise and specialties, such as the RDI/WHO Global Network for Rare Diseases, which aims to connect experts, clinics, expert centers, and patient organizations globally.[19]

HEALTH SYSTEM BARRIERS AND OPPORTUNITIES

Barrier 3: Challenges around appropriate value assessment for gene therapies

The value of a particular gene therapy for reimbursement and access will depend on multiple factors. Some factors include safety, efficacy, the durability of clinical benefits, the size of the treatable population, and the financial impact on health systems and patients. However, substantial outcome uncertainty for gene therapy may exist due to the small number of patients and resulting sample sizes of clinical trials, the absence of an appropriate standard of care for comparison, and the potential long-term benefits. There are also concerns about the budget impact of these therapies and the financial sustainability of health systems.

Traditional health technology assessment (HTA) methodologies for assessing value and making reimbursement decisions may find it difficult to manage this uncertainty. These assessments may not fully recognize gene therapy's value for rare genetic diseases. The potential broader benefits of gene therapy for rare genetic diseases to health systems and society may be overlooked and undervalued by the current HTA methods. These shortcomings include the decreased total expenditures resulting from potentially one-time or short treatment regimens, the value of hope (i.e., some patients may value a treatment that provides a chance for long-term survival, hoping that they will get to live longer)[5,20] and the spillover effects on caregivers and family. As a result, current HTA and evidence-generating methods will need to evolve or transform to fully realize the potential of gene therapies and facilitate patient access.[21] There are efforts underway from some HTA bodies to incorporate and recognize additional elements of value that pertain to gene therapy. However, these outcomes have yet to be actualized in current assessments. As this is a dynamic space, improvements in value assessment are anticipated as more gene therapies are brought through the review process.

Opportunities:

Engage in Early Dialogue:

- Develop a formal process for early dialogue among payers, HTA bodies, and manufacturers to align on appropriate assessment criteria, projected long-term real-world data needs, and feasible evidence packages. This would acknowledge the more limited data available during the launch due to smaller patient populations, clinical trial limitations, and high unmet need.

Review Value Assessment Methodologies to Ensure Processes are Fit for Gene Therapies:

- Develop processes for the post-launch generation of robust real-world evidence to alleviate uncertainties around long-term efficacy and safety.
- Develop transparent standards that include real-world evidence and surrogate endpoints in assessments.

- Incorporate methods to recognize the potential long-term benefits of gene therapies for rare genetic diseases by including a lifetime perspective in modeling and appropriate discount rates in budget sensitivity analyses.
- Operationalize additional elements of value for patients, families, health systems, and society as part of the HTA decision-making process within value assessment based on continued research.
- Further develop methods for indirect comparisons.

Support Multi-Stakeholder Models of Advanced Therapy Medicinal Product (ATMP) Development:

- Explore the possibilities of bringing together multiple stakeholders to develop ATMPs (e.g., academic, non-profit entities, etc.) to address sustainability and affordability. For example, the Paul-Ehrlich-Institut has established a program to provide early regulatory support to European academic ATMP developers.[22]

Barrier 4: Challenges for the adoption of innovative financing models

Gene therapy requires novel approaches to financing. The potentially one-time approach of gene therapies for rare genetic diseases may necessitate payers shifting away from the more familiar 'pay-per-prescription' model of traditional chronic therapies upon which most existing payment mechanisms are based. Many of the same uncertainties that pose challenges for assessing value appropriately during reimbursement decisions also make it difficult for health systems to pay the upfront prices of some gene therapies while sustaining healthcare budgets. To address concerns regarding affordability and clinical uncertainty, novel payment models that spread payment over time and link to real-world outcomes can help payers manage the budget impact and sustainability of health systems while rewarding and recognizing the value of innovation.[5]

However, these novel payment models are complex and may require new frameworks and infrastructure. In many countries, policymakers must update their legal and regulatory frameworks and accounting rules. Conventional accounting rules usually require the payer to accrue the full payment of medicine in the year of purchase, thus eliminating the income statement benefits of spreading the financial costs over time to balance the benefit accrual. Further, standard processes and technical infrastructure data will be required to monitor and evaluate long-term safety and outcomes tied to payment models and reimbursement decisions and to help keep track of patients over time and as they move across payers or health systems. Accurate data is also critical for modeling the financial impact of gene therapy for rare genetic diseases on future health budgets, including long-term cost savings to patients and health systems. However, novel financing frameworks, such as amortization and operational guidelines, are already being used in some regions, notably the USA and Europe.[23]

Opportunities:

Support Horizon Scanning and Education:

- Engage in early informal dialogue with policymakers and payers to educate them on the science behind new technologies, upcoming pipelines, and potential value to patients to facilitate budget planning for gene therapies. An example is the work currently being done by the American Society for Gene & Cell Therapy (ASGCT), which aims to provide high-quality, science-based, independent education to federal policymakers.

Support the Use of Novel Payment Models:

- Update legal and regulatory frameworks and accounting rules to accommodate the dynamic and multi-year nature of value-based agreements and other novel payment models.
- Pilot pay-for-performance, pay-for-response, or other innovative outcomes-based agreements for gene therapies and collect learnings that can be implemented across markets. These could also include “risk-sharing” agreements as additional evidence of effectiveness and cost-effectiveness are collected.
- In parallel, implement financing schemes that reduce up-front costs. In Italy, a recent example of an innovative financing mechanism included a fund that is operated using savings generated by advanced therapy medicinal products.
- Develop a technical framework and appropriate data infrastructure to collect and measure real-world outcomes.
- Exchange and share best practices around effective, innovative financing frameworks across health systems.

CONCLUSION

Gene therapies can potentially transform the lives of people living with devastating rare genetic diseases. They offer hope to patients, families, and caregivers, many of whom have almost no other options for addressing the chronic, progressive, disabling, and often fatal effects of their conditions. This new treatment paradigm also has the potential to transform health systems and societies more broadly—from the way stakeholders think about the value of life science innovation and the return on investment in health, to how they work towards achieving universal health coverage and leaving no one behind. The time is now for stakeholders from across sectors, government, and borders to work together to ensure that health systems are ready to help realize the potential of gene therapies fully, sustainably, and equitably for patients.

When countries can address existing barriers to sufficient infrastructure for rapid and accurate rare disease diagnosis, delivery of gene therapy to eligible patients, and implementation of appropriate value assessments and innovative reimbursement models, they will be able to better facilitate care delivery and access to gene therapy. It is important to note that critical to the success of these opportunities will be the collection and utilization of real-world evidence (RWE) as a governance tool to measure effectiveness and inform ongoing improvements to care delivery and access.
To surmount the various complex health system barriers, countries can implement the potential opportunities offered in this Framework at the level and scale appropriate for their current levels of readiness and health system priorities. Patients will be the ultimate and most important beneficiaries of such efforts, and they also need to be included as co-leaders and co-creators.

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