

Written Testimony
Of
Terence Flotte, MD
Vice President of the American Society of Gene and Cell Therapy

United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health
RE: "Legislative Proposals to Support Patients with Rare Diseases"

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Washington, DC

Chairman Guthrie, Vice Chair Bucshon, Ranking Member Eshoo, and Members of the Subcommittee, thank you for the opportunity to testify on behalf of the American Society of Gene & Cell Therapy (ASGCT). I am Dr. Terence Flotte, Provost and Dean of the University of Massachusetts Chan Medical School, and Vice President of ASGCT. The Society is a nonprofit professional membership organization comprised of more than 6,200 members. Working in settings such as universities, hospitals, and biotechnology companies, these members are scientists, physicians, patient advocates, and other professionals working together to advance the field of gene and cell therapy.

The mission of ASGCT is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease. ASGCT's strategic vision is to be a catalyst for bringing together diverse stakeholders to reshape the practice of medicine by incorporating the use of these transformative therapies. Many of ASGCT's members, like myself, have spent their careers in this field performing the underlying research that has led to today's robust pipeline of cell and gene therapies (CGTs).

America is clearly the world leader in gene therapy, both in terms of pioneering gene therapy science and technology and in the application of gene therapy to human diseases. ASGCT represents many of the scientists, physicians and regulatory professionals from academia, industry and government who have propelled the US into this leadership position. These therapies are transformational and, as such, they have challenged the treatment and payment paradigms of our health care system.¹ My professional experience is rooted in being a physician researcher, and my testimony today will focus on research, product development, regulatory issues, and the patient experience.

¹ The Society supports policies that foster the adoption of, and patient access to, new therapies. However, ASGCT's support *does not* imply a position on any individual pricing, coverage, or reimbursement decisions.

I have always felt passionate about patients' access to health care; this drove me to pursue a career in medicine. After finishing my medical degree and residency in pediatrics, I pursued and completed a pediatric pulmonary fellowship and postdoctoral training in molecular virology. In 1995 I led the first team of researchers to use the adeno-associated virus, better known as AAV, to deliver corrective genes to targeted sites in the body, including the damaged airways of adults with cystic fibrosis. AAV vectors are now one of the basic building blocks of today's gene therapy products. I have conducted numerous clinical trials and am currently investigating the use of gene therapy for genetic diseases, including alpha-1 antitrypsin deficiency and Tay-Sachs disease. My life's work has been in the rare disease space, and I am honored to be here with you and the esteemed members of the committee to discuss these important issues.

Gene Therapy Development Pipeline

There are over 10,000 rare diseases,² up to 80% of which can be traced to mutations or changes in a single gene.³ Early in my career, clinicians had few therapeutic options to offer these patients. But now, breakthroughs in gene therapy are enabling patients with a handful of genetic diseases to live and thrive. Gene therapy aims to address the underlying cause of disease, such as gene mutations, through new genetic material. If you think of genes as the blueprint to our bodies, gene therapy can fill in missing parts and/or correct errors in the drawings. This new genetic material, such as a working gene, is delivered into the patient's cells using a vector. A vector is like a package used to deliver a specific message. Vectors, with the genetic information they carry, can directly target the cause of a disease, and change the way a cell functions. In addition, they typically only need to be administered once and can be used for rare inherited diseases that have few to no other treatment options available.

² National Center for Advancing Translational Sciences (2023). *Our Impact on Rare Diseases*. <https://ncats.nih.gov/research/our-impact/our-impact-rare-diseases>

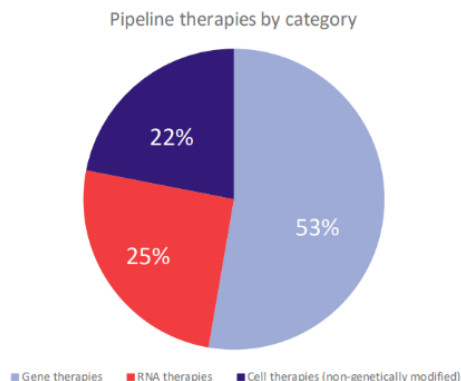
³ Blencowe, H., Moorhithie, S., Petrou, M., Hamamy, H., Povey, S., et. al. (2018). *Rare Single Gene Disorders: Estimating Baseline Prevalence and Outcomes Worldwide*. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6167259/>

In 2023, the pipeline of gene, cell, and RNA therapies grew by 6%.⁴ As a result, there are 3,951 such therapies in development, ranging from preclinical through pre-registration (filing for regulatory approval).

Pipeline of gene, cell, and RNA therapies

3,951 therapies are in development, ranging from preclinical through pre-registration

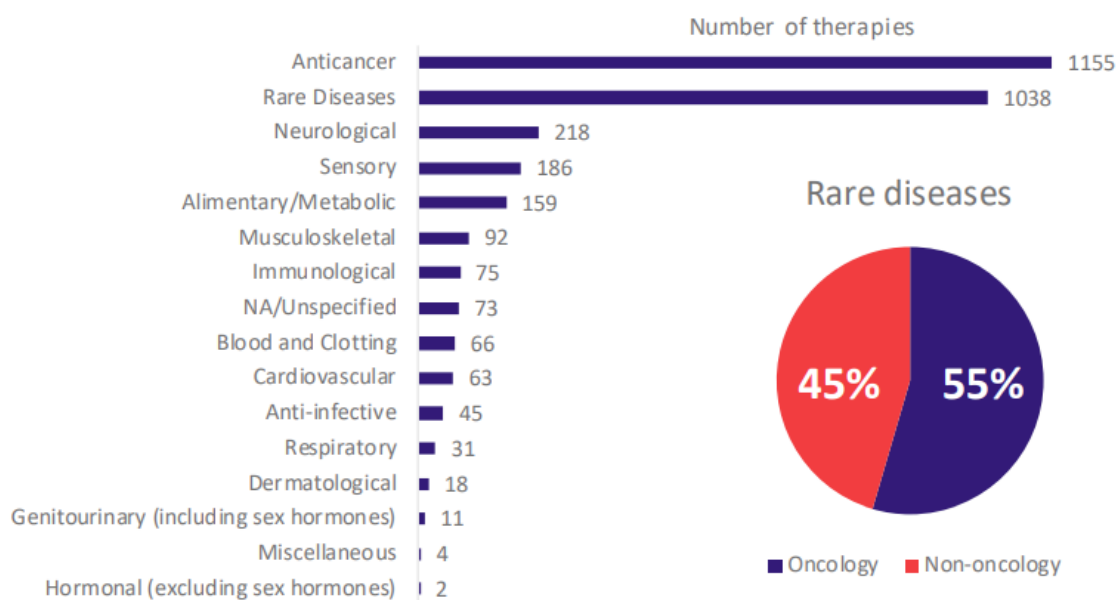
- 2,111 gene therapies (including genetically modified cell therapies such as CAR T-cell therapies) are in development, accounting for 53% of gene, cell, and RNA therapies
- 878 non-genetically modified cell therapies are in development, accounting for 22% of gene, cell, and RNA therapies



Currently, oncology and rare diseases are the top areas of gene therapy development in both the overall pipeline (preclinical to pre-registration) and in the clinic (Phase I to pre-registration). As a pediatric subspecialist diagnosing and treating patients with rare genetic diseases, I have had very difficult discussions with parents looking for medical help to treat their children.

⁴ American Society of Gene and Cell Therapy (2023). *Gene, Cell, and RNA Therapy Landscape Report: Q4 Quarterly Data Report*. <https://asgct.org/global/documents/asgct-citeline-q4-2023-report.aspx>

Number of therapies from preclinical through pre-registration



The challenge facing clinicians now is that parents see gene therapy helping children with different rare diseases, and are asking “*Why can’t you do that for my child?*” We are faced with the challenge of applying gene therapy science and technologies to each of these thousands of individual rare genetic diseases. Ultimately, we want to do everything we possibly can to provide greater access to gene therapy for every patient.

To a certain extent, development challenges are a result of real-world limitations. Each genetic disease essentially requires a different product, even with use of the same gene therapy vector. In addition, specific diseases vary in which organs and cell types need to receive the corrective gene. For some diseases it is the liver, the brain, or spinal cord, and for others it is the eye or the muscle. Additionally, while the statutory requirements for marketing approval for drugs to treat rare and common diseases are the same, drug development is often more difficult to address in the context of a rare disease. There is often limited medical and scientific knowledge,

natural history data, and drug development experience. This is why robust research is needed to help close the knowledge gap.

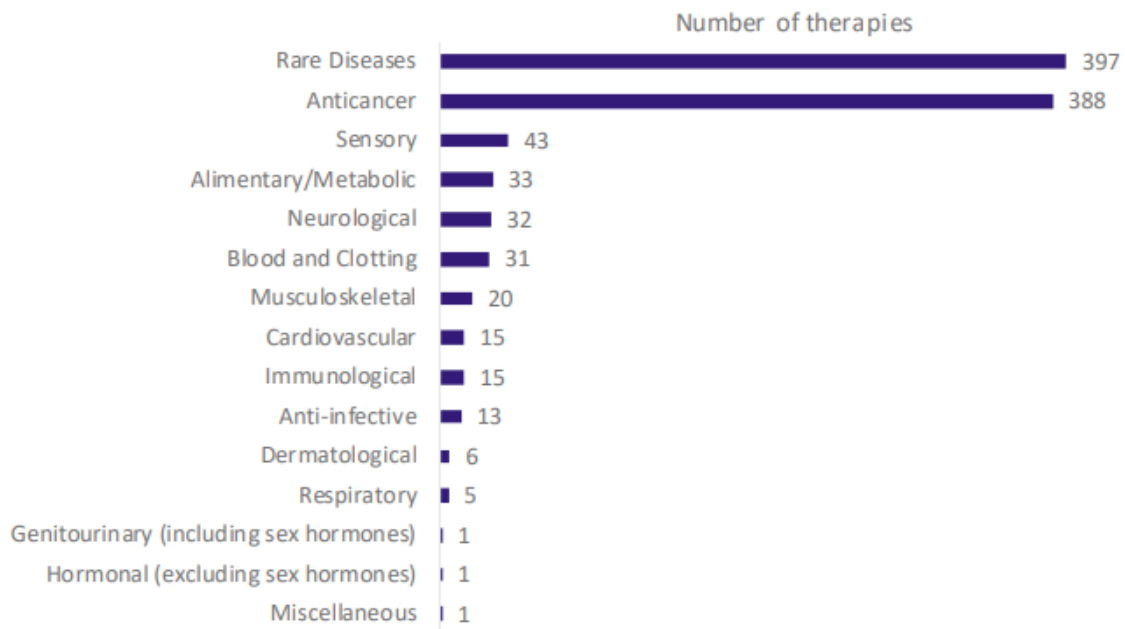
Investments in Research & Development

In the US, 10 percent of the population is affected by rare disease; and 95 percent of patients have no current treatment options.⁵ As evidenced by the development pipeline, gene therapy offers great promise for people with rare inherited disorders. As genetic mutations for rare diseases continue to be identified, there is also a greater need for funding to support translational research – bridging studies which help advance potential new gene therapy approaches toward clinical research. While there are more therapies for rare diseases in the clinic,⁶ there remains a great scientific need to investigate the *preclinical* application of gene therapies to treat new diseases and improve the design of vector technologies. Continued investments in basic, translational, and early clinical research on rare diseases is needed to build the scientific underpinnings of gene therapy. ASGCT supports robust funding for the National Institutes of Health (NIH) to ensure the US remains a global leader in medical innovation.

⁵ Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development (2010). *Rare Diseases and Orphan Products: Accelerating Research and Development*. www.ncbi.nlm.nih.gov/books/NBK56189

⁶ American Society of Gene and Cell Therapy (2023). *Gene, Cell, and RNA Therapy Landscape Report: Q4 Quarterly Data Report*. <https://asgct.org/global/documents/asgct-citeline-q4-2023-report.aspx>

Therapies in the clinic (excludes preclinical development)



A significant barrier to the development of commercialized gene therapies for small populations are the costs and logistics associated with product development. The limited patient pool can be an impediment to clinical trial enrollment and the commercial viability of products, especially those that would be used in less than approximately 100 individuals each year; this can pose a serious challenge to the development of treatments for these ultra-rare diseases.⁷ ASGCT is a founding member of the Bespoke Gene Therapy Consortium,⁸ a public and private partnership. Led by the Foundation for the NIH, this partnership aims to fund research on gene therapy for 5-6 ultra-rare diseases using a standard menu of vectors, vector manufacturing processes, delivery methods, and clinical protocols, to advance them into the clinic. The development of standard protocols may ultimately help streamline gene therapy development and accelerate access for countless patients.

⁷ Marks, P., Witten. C. (2020). *Toward a new framework for the development of individualized therapies*. <https://www.nature.com/articles/s41434-020-0143-y>

⁸ National Institutes of Health (2024). *Accelerating Medicines Partnerships (AMP): Overview*. <https://www.nih.gov/research-training/accelerating-medicines-partnership-amp>

Private sector investments play a critical role in the development of gene therapies and have provided a vital source of funding and expertise for the advancement of gene therapy to patients. However, this investment is predicated on regulatory and market certainty. Biotechnology companies have taken on the risks and challenges of gene therapy development programs because of the great promise for patients and the environment established by the Orphan Drug Act to distinguish these products from their peers. I have had many experiences working hand in hand with industry partners on clinical trials. While some of these have succeeded, others have failed – either for scientific reasons or funding challenges. I cannot tell you how disappointing that is to patients and families with those diseases. Maintaining a favorable investment and research environment is critical for the pipeline's continued growth and success.

Clinical Trials

Gene therapies are often developed for the treatment of rare diseases with high unmet need. As a function of being a rare disease, this can limit clinical trial size and duration. As a result, gene therapy trials may have Phase I and II trials of 5 – 20 patients for initial dose-finding and efficacy. This is significantly smaller than trials for common diseases. Fortunately, gene therapies often demonstrate efficacy early in development; promising results can be seen as early as Phase I. With the potential to aid countless patients, it is imperative to work expeditiously to meet this significant unmet need for diseases that often have high childhood mortality rates.

Keeping in mind the small patient populations, alternative study designs – including decentralized studies, use of RWE (Real World Evidence), and patient experience data – are

crucial in advancing CGT research.⁹ Clinical trials for CGT products often require specialized infrastructure, manufacturing, and clinical administration facilities, which can further limit patient participation in a traditional trial structure but may be mitigated by innovative trial approaches. Embracing these approaches can benefit patients in need by allowing researchers to accelerate the development and adoption of innovative CGTs and make participation more accessible for a broader, and more representative, population.

Incorporating decentralized study designs can aid researchers in gathering data from patients in their natural environments, which may provide a more accurate assessment of treatment outcomes and long-term safety. RWE can complement the findings from controlled clinical trial settings, enhancing the overall understanding of the therapy's impact. Innovative study designs can also offer a more patient-centered, and efficient way to collect pre- and post-approval safety and efficacy data, ultimately leading to better treatment outcomes.

Traditional clinical trials may face challenges in recruiting a diverse range of participants due to geographical limitations or lack of awareness, and these issues are heightened in rare disease trials. Some of the disparities in clinical trial participation, and lack of representation in clinical data, stem from logistical barriers (such as lack of transportation, interference with work and family responsibilities, as well as out-of-pocket expenses). RWE, such as RWE derived from registries, has the potential to facilitate the inclusion of more representative patient populations to reflect the risks and benefits of products more accurately.^{10,11} These same considerations

⁹ American Society of Gene and Cell Therapy (2023). *Comments to FDA on Methods and Approaches for Capturing Post-Approval Safety and Efficacy Data on CGT Products Listening Session*. <https://asgct.org/advocacy/policy-statement-landing/2023/post-approval-cgt-products-listening-session>

¹⁰ American Society of Gene and Cell Therapy (2023). *Comments to FDA on Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Draft Guidance*. <https://asgct.org/advocacy/policy-statement-landing/2023/considerations-for-the-design-and-conduct-of-exter>

¹¹ American Society of Gene and Cell Therapy (2022). *Comments to FDA on Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Draft Guidance*. <https://asgct.org/ASGCT/media/about/ASGCT-comments-on-FDA-2021-D-1146-Assessing-Registries.pdf>

also are relevant in the post-approval setting, especially for patients living in remote areas who may be less likely to travel to tertiary institutions.

Regulatory Challenges & Incentives

Among the rare disease population, around half impact children; the United States alone has approximately 15 million pediatric rare disease patients.¹² The widespread adoption of whole genome sequencing to diagnose these patients means that families of those children may know exactly what gene is causing the problem in their child. The CGT pipeline offers a unique opportunity to address many of these diseases for which there are currently no good treatment options.

I often receive emails from families telling me about the gene defect that has caused disease in their baby. In those instances, parents are looking for an active clinical trial. The gene defect described by these parents almost never originates within one of the handful of genes for which there is an approved therapy and in all too many cases is one of the thousands of genes for which a therapy is not yet in development. As a result, families often become active in raising money to develop the therapy themselves. Because these diseases usually cause shortened life spans, the parents' effort becomes a "race against the clock" to raise the money and recruit the research and clinical teams needed to develop a treatment for their child. Unfortunately, and all too often, the time and money needed to move from gene discovery to an effective therapy proves to be too great for the families to surmount.

With all those challenges, *how can we accelerate this path from gene discovery to treatment and make these challenges easier to overcome?* Without a doubt, given the unique nature of

¹² United States Government Accountability Office (2021). *Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial*. <https://www.gao.gov/assets/gao-22-104235.pdf>

these treatments and the high failure rates, regulatory flexibility and incentives are needed to encourage and accelerate private sector investments in rare disease therapies.

For instance, the Pediatric Priority Review Voucher Program grants the sponsor of a product for a rare pediatric disease a voucher can be redeemed to receive a priority review of a subsequent drug.¹³ That voucher can be used by the original sponsor or sold to help offset the cost of product launch. This program is unique in that it is a government incentive but does not use government dollars. This is a win for product developers, patients, and taxpayers. The pediatric PRV program sunsets this year on September 30th. I humbly encourage the committee to reauthorize it in a timely manner. Certainty is paramount for investment and development decisions and this program is needed to help accelerate development in the rare disease space.

Our goal is to work collaboratively with FDA to create a regulatory framework that encourages and supports the development and availability of these treatments for rare diseases. FDA has made great strides; however, there is more work to do to ensure that the regulatory system keeps pace with the science and innovation that drive the development of CGTs while ensuring patient safety and product quality. Areas where ASGCT believes there should be greater consideration of regulatory flexibility include, but are not limited to, the following:

Pre/Nonclinical Development:

Clarity on regulatory expectations is needed regarding the extent to which nonclinical studies conducted on one product can be leveraged to support related or similar technologies. For example, when a cell or gene therapy product employs the same manufacturing platform with only the transgene being modified, there is a potential

¹³ Voucher users are required to pay FDA priority user fees.

opportunity to leverage previous safety studies; these are typically conducted in a non-disease state animal model. However, it is uncertain if FDA is open to a risk-based approach to leveraging prior safety data.

The Society has requested clear guidance on this risk-based approach and whether specific elements of a nonclinical safety package are more likely to be acceptable for data leveraged from similar products. Naturally, the acceptance will also depend on how the different transgene affects the product's activity. Nevertheless, there is significant opportunity, especially when dealing with safety studies conducted in non-diseased or naïve animal model systems.

The Society has also requested guidance from FDA regarding the expectations for preclinical testing alternatives when relevant animal models are not available. In these situations, leveraging safety testing through non-disease state models and *in vitro* modeling should be considered. In some instances, embracing alternative methods may help reduce preclinical development time and provide more accurate predictions of human safety. Overall, ASGCT believes that clarity on regulatory expectations for alternative testing methods is crucial and research, development, and science-based adoption of such alternatives should be prioritized.

Clinical Data:

Interpreting clinical data in the context of rare diseases and individualized treatments presents unique challenges. There is a pressing need for clarification regarding the interpretation of clinical data in conditions where the natural history of the disease is lacking, and/or the disease exhibits significant heterogeneity, all of which are often the case for rare diseases. FDA's draft guidance *Considerations for the Design and Conduct*

*of Externally Controlled Trials for Drug and Biological Products*¹⁴ emphasized the need for randomized control trials (RCTs) due to disease heterogeneity. While we in the research community agree that RCTs are the gold standard, they are sometimes not feasible and/or ethical in certain populations, for instance when the population is extremely small, or the disease is rapidly fatal. The guidance failed to provide critical details about how much data can be leveraged from natural history studies or RWE when the disease progression is not well understood, and whether FDA will accept such data as a control in studies. It is crucial for development programs to understand when natural history data may be appropriate and when RCTs are required, particularly for rare diseases.

Manufacturing:

As more CGT products receive FDA licensure and approval, improvements will be critical to meet real-world patient demand, bring manufacturing closer to the bedside, and reduce production costs. New innovations in manufacturing have lagged behind other areas in the field. One reason for this delay is the lack of market incentive to develop new products or manufacture approved ones using a novel technology with inherent regulatory risk. The National Academies of Medicine published a report¹⁵ in 2021 which suggested that FDA implement a pathway to review novel advanced manufacturing technologies separately from individual products to de-risk their use in product applications. ASGCT appreciates that Congressmen Carter, Soto and members of this Committee, along with their counterparts in the Senate, established the Advanced Manufacturing Technologies (AMT) Designation Program in the Food and Drug Omnibus

¹⁴ Food and Drug Administration (2023). *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry*. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products>

¹⁵ National Academies of Sciences, Engineering, and Medicine (2021). *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations*. <https://doi.org/10.17226/26009>

Reform Act (FDORA).¹⁶ If implemented properly, the program could help address the challenges currently facing the manufacturers and sponsors of CGTs and alleviate workload on FDA reviewers who currently need to understand and assess bespoke manufacturing processes for each CGT. ASGCT is concerned that the current implementation plan outlined by FDA in its recent guidance document¹⁷ limits the use of this pathway for CGTs.

The Society was pleased with the FDORA provision directing FDA to create a platform technology designation program. This provision defines a “platform” technology and allows those who are granted the designation to receive additional assistance from FDA, similar to what’s available for Breakthrough Therapies.¹⁸ Platform technologies have the potential to streamline gene and cell therapy development by allowing a single technology, such as a nucleic acid sequence or a vector, to be utilized across multiple products. Once a product using a designated platform is approved, follow-on products should be explicitly permitted to reference data from the earlier application, and manufacturing changes to the platform can be done in a single supplemental application for all drugs on such platform. Again, if FDA follows congressional intent this designation would ultimately help patients access CGTs faster.

Safety and Efficacy:

In small patient and clinical trial populations, obtaining statistical significance of effects can be challenging – even if the clinical benefit seems clear to a physician, patient, or

¹⁶ United States Congress (2023). *Consolidated Appropriations Act (H.R.2617)*. <https://www.congress.gov/bill/117th-congress/house-bill/2617>

¹⁷ Food and Drug Administration (2023). *Advanced Manufacturing Technologies Designation Program: Guidance for Industry*. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/advanced-manufacturing-technologies-designation-program>

¹⁸ Food and Drug Administration (2018). *Breakthrough Therapy Designation*. <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy>

their family. Especially in the context of CGTs for rare diseases, greater regulatory flexibility is needed. For instance, the development and linkage of how well a product works via *in vitro* assays (known as product potency) to patient outcomes becomes significantly more challenging in small clinical trials. It is not always clear that a good result at the bench directly translates to a good result at the bedside. FDA is currently evaluating its approach to potency assays,¹⁹ and we hope that the agency uses this as an opportunity to explore whether different expectations can apply for rare disease products. In a forthcoming comment letter, ASGCT will recommend a focus on confirming manufacturing consistency from product lot to lot, rather than having additional potency tests directly tied to patient outcomes for smaller, accelerated clinical development plans.

Additionally, information on patient experience is critical. FDA should be given credit in this respect for engaging with patients and families in a very effective way, in sessions called patient-focused drug development meetings. Patients and patient advocates highly value these sessions, where their voices are heard regarding which outcomes of trials are most valuable to them. FDA must provide a statement after drug approval about the patient experience data submitted, and reviewed, with the sponsor's Biologics Licensing Application (BLA) or New Drug Application (NDA). This provision, passed as a part of 21st Century Cures,²⁰ has provided the community with some transparency as to when patient experience data is being considered. In my professional experience, assessing patient experience has been extremely beneficial. Understanding how patient

¹⁹ Food and Drug Administration (2023). *Potency Assurance for Cellular and Gene Therapy Products: Draft Guidance for Industry*. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/potency-assurance-cellular-and-gene-therapy-products>

²⁰ United States Congress (2016). *21st Century Cures Act (H.R.34)*. <https://www.congress.gov/bill/114th-congress/house-bill/34>

experience is being used in risk-benefit assessments for CGT products could be very helpful.

Addressing the challenges and opportunities of interpreting clinical data for rare diseases and CGTs requires flexible approaches and collaborative efforts to enhance safety and efficacy assessments. As one example, I will describe how a gene therapy for a rare genetic cause of blindness received FDA approval. Patients with this genetic disorder first lose the ability to see in dim light. When the first patients in an initial clinical trial were treated, the investigators found the patients could navigate in dim light without running into furniture or other obstacles. This is not a function that is typically evaluated in ophthalmology trials. Working hand in hand with FDA regulators under the leadership of Dr. Celia Witten and Dr. Peter Marks, of the FDA Center for Biologics Evaluation and Research (CBER), the sponsor and physicians involved in the gene therapy program developed a completely new test called the multi-luminance mobility test (MLMT).²¹ This test demonstrated the effect that the patients were experiencing in a robust and reliable manner that aligned with the ophthalmology field's experience with functional vision. The MLMT was the critical proof of effectiveness that resulted in FDA approval of that gene therapy – it was the first in vivo gene therapy to ever be approved in the US. In addition to proving the benefit of that one product, this achievement proved the paradigm that patient experience could be assessed in an objective way that met the long-standing FDA standard of a safe and effective therapy.

²¹ Chung, D., McCague, S., Yu, Z., Thill, S., DiStefano-Papper, K., et. al. (2017). *Novel Mobility Test to Assess Functional Vision in Patients With Inherited Retinal Dystrophies*. <https://pubmed.ncbi.nlm.nih.gov/28697537/>

Conclusion

In closing, I want to express my thanks to the members of the committee for inviting me to testify today on behalf of the American Society of Gene and Cell Therapy. In our view, the progress achieved for patients in the CGT field, since the Human Genome Project, is one of sciences' greatest achievements of our time. Scientists and physicians have an obligation to do everything in their power to help patients and families living with rare genetic diseases. Progress in this area is wholly dependent on active collaboration amongst scientific disciplines, universities, hospitals, biotechnology companies, and government. It is also dependent on Congress continuing to robustly fund biomedical research in academia, supporting effective incentives for private sector investment, and ensuring FDA has appropriate review processes in place for expediting safe and effective cures to our most vulnerable rare disease patients.