June 22, 2021

Joni L. Rutter, Ph.D.
Acting Director
National Center for Advancing Translational Sciences
6701 Democracy Boulevard
Bethesda MD 20892

Re: NOT-TR-21-027

Request for Information (RFI): Facilitating the Early Diagnosis and Equitable Delivery of Gene-Targeted Therapies to Individuals with Rare Diseases

Dear Dr. Rutter:

The American Society of Gene and Cell Therapy (ASGCT) appreciates the opportunity to provide information to NCATS on the significant issues of early diagnosis and equitable delivery of gene therapies to those with rare diseases. ASGCT is a nonprofit professional membership organization comprised of more than 4,500 scientists, physicians, and other professionals working in gene and cell therapy in settings such as universities, hospitals, and biotechnology companies. A core portion of the Society’s mission is to advance the discovery and clinical application of genetic and cellular therapies to alleviate human disease.

Because NCATS and the stakeholders contributing to NCATS’ work groups have a great deal of expertise about these topics, ASGCT is providing responses to the portions of this RFI that may best build upon existing knowledge. In addition, the Society is sharing the policy solutions that it supports related to these issues.

ASGCT defines gene therapy as the introduction, removal, or change in genetic material—specifically DNA or RNA—into the cells of a patient to treat a specific disease. Therefore, in these comments, we use the term gene therapy to refer to all gene-targeted therapies, except when otherwise noted to distinguish RNA therapies from other types of gene therapy.

1. **To develop infrastructure for the efficient, effective, and equitable distribution of therapies it is important to define the following:**

   **Who are the individuals who could benefit from gene-targeted therapies, now and in the future?**
The development of, and accessibility to, gene therapies for all individuals with rare diseases who may benefit from them is of paramount importance to ASGCT. These topics are significant even for diseases that have other treatment options available that manage symptoms associated with a condition, because gene therapies may halt disease progression by addressing the genetic cause of disease. To guide infrastructural development to accommodate the robust pipeline of these therapies, the Society highlights below the status of gene therapy development.

The individuals with rare diseases who are now benefiting from FDA-approved gene therapies (excluding RNA therapies) are those with confirmed biallelic RPE65 mutation-associated retinal dystrophy with viable retinal cells as determined by the treating physician, and those less than two years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.¹ The individuals with rare diseases who are now benefiting from FDA-approved RNA therapies are those with the following conditions: homozygous familial hypercholesterolemia; Duchenne muscular dystrophy; transthyretin-related hereditary amyloidosis; porphyria; and hyperoxaluria.¹

The preclinical and clinical development pipeline is indicative of the categories of rare diseases that are more likely to benefit from gene therapy in the shorter term. According to ASGCT’s landscape report issued in April 2021,¹ the non-oncology diseases most targeted by gene therapy preclinical and clinical studies (excluding RNA therapies) include unspecified neurological diseases, unspecified ocular disorders, retinitis pigmentosa, hemophilia A and B, amyotrophic lateral sclerosis, sickle cell disease, cystic fibrosis, unspecified autoimmune diseases, Duchenne muscular dystrophy, thalassemia, Batten disease, Gaucher disease, frontotemporal dementia, Huntington’s disease, and Leber’s congenital amaurosis. The non-oncology indications most targeted by RNA therapies include Duchenne muscular dystrophy, neurological disease, hepatitis B, hepatic dysfunction, and alimentary/metabolic diseases.

When is the optimal time to identify individuals who could benefit from gene-targeted therapies?

The optimal time to identify individuals with genetic diseases is as soon as possible. Early diagnosis is especially important for therapies where there may be irreversible damage, which can be prevented by early intervention (e.g., for rapidly progressing disorders, such as mucopolysaccharidosis II (MPS II), metachromatic leukodystrophy (MLD), Sanfilippo disease, and Batten disease, in which early diagnosis is possible before patients are symptomatic). A diagnosis provides patients with critical advantages to manage their disease, even if there is no FDA-approved or licensed therapy specifically for that disease. Those benefits include receiving referrals to specialists for proper medical management with drug and non-drug therapies (e.g., PT and OT), connecting with the patient community, and enrolling in clinical trials for new therapies or those that assess the natural history of the disease.

ASGCT is supportive of the Newborn Screening Program which provides funding and recommendations for states to screen babies for “actionable” genetic diseases. The Advisory

Committee on Heritable Disorders in Newborns and Children (ACHDNC), within the Health Resources and Services Administration (HRSA), establishes the Recommended Uniform Screening Panel (RUSP), which lists the conditions that states must aim to screen for in order to qualify for certain federal funding.

Newborn screening programs across the United States could be greatly improved by expediting the process for adding conditions to the RUSP in the following ways:

- **Enable the development, validation, and dissemination of screening tools.** Development of new screening tools is paramount for inclusion on the RUSP. Where testing is available and validated, it can be used by providers to more quickly identify patients and families who may be at greater risk of suffering from a rare genetic disease.
- **Ensure the RUSP keeps pace with treatment approvals.** While we appreciate that the testing infrastructure needs to be evaluated as well, there should not be a delay in informing states, parents, and physicians that testing for and diagnosing a disease has become actionable as soon as the first treatment has been approved or licensed. We also believe, given the advantages of early diagnosis mentioned above, that “actionable” conditions should not be limited to those with an approved therapy.
- **Collaborate with and rely upon FDA.** The ACHDNC should ensure that nominating groups are not being charged with collecting data that are redundant to that which FDA has already reviewed. ASGCT also recommends that the ACHDNC collaborate with FDA to the maximum extent possible under current law.
- **Ensure the process to advance a disorder through the ACHDNC is transparent, predictable, and timely.** Additional guidance documents on standards and allowable collaborations could provide assistance with required data collection.

In 2021, ASGCT has supported state-level efforts in Georgia and Ohio to consider adoption of additional conditions on the RUSP within a reasonable time frame, with the necessary funding for adding the conditions.

2. **Consider what type of infrastructure is required to disseminate gene-targeted therapies to individuals with rare diseases in need of treatment using the following:**

   **What are the current mechanisms and infrastructure for diagnosing and identifying individuals with rare diseases for gene-targeted therapies?**

   **How can the early diagnostic process be improved to create the type of infrastructure required to disseminate gene-targeted therapies to individuals with rare diseases in need of treatment?**

   For rare conditions that are not screened for at birth, the process for diagnosis is often a long odyssey that prevents individuals from accessing critical medical services, community, and clinical investigations (discussed above). While this is true across payers, it is especially difficult in the Medicaid population, which often has limited access to specialized services and testing. Whole genome and whole exome sequencing are critical tools for diagnosing rare diseases. To
this end, ASGCT supports expanding Medicaid coverage for whole exome and whole genome sequencing to facilitate earlier diagnosis and improve equitable access.

Another important factor is engaging in both disease-specific and broad education campaigns among health care providers given their critical role in facilitating early diagnosis. Plain language summaries can be critical for equipping patient communities (e.g., patients and caregivers) and educating them regarding accurate diagnosis and management of their condition.

**What other models can be developed and used to better identify individuals who can benefit from rare disease therapies in a timely manner?**

ASGCT believes that answers to this question will be identified through the ongoing multi-stakeholder effort in which a Newborn Screening Modernization Consortium is providing direction to the Research Triangle Institute Genomics, Bioinformatics, and Translational Research Center (RTI Center) to complete a Newborn Screening Modernization Research Assessment. ASGCT has staff representation on the Newborn Screening Modernization Advisory Board, which advises the consortium. This project will complete an assessment that identifies the limitations in the current NBS system in addressing the timely diagnosis of all newborns who may benefit from new treatments, as gene therapy development rapidly expands.

**Are there any public/private partnerships that support gene-targeted therapies?**

The Accelerating Medicines Partnership in Gene Therapy, including the Bespoke Gene Therapy Consortium, which NCATS is co-leading is a public/private partnership that will support gene therapy development for ultrarare conditions. The Society supports this effort and encourages establishing further partnerships to advance development in the sector as a whole. Additional solely public efforts that support gene-targeted therapies, described below, could inform potential future public/private partnerships.

The Regenerative Medicines Innovation Project (RMIP), run by NHLBI, requires matching funds for the research grants it awards in regenerative medicine. ASGCT has recently highlighted that gene therapy is a type of regenerative medicine via the TRANSPLANT Act, which reauthorizes the C.W. Bill Young Cell Transplantation Program. The legislation includes ASGCT-recommended language to codify attention to regenerative medicine into the Public Health Service Act (PHSA) and to explicitly include gene therapies and genetically-modified cells in the definition of regenerative medicine. ASGCT also worked to elevate the need for continued funding of the RMIP after 20th Century Cures Act funding of the project expires.

In addition, the Somatic Cell Genome Editing Consortium (SCGE), funded by the NIH Common Fund, is working to create a genome editing toolkit that would provide broadly accessible data, tools, systems, and assays that could enable a more open-access approach for clinical development of gene editing technologies. ASGCT is pleased to see that the Ultra-rare Gene-based Therapy (URGenT) program of the National Institute of Neurological Disorders and Stroke (NINDS) will soon be supporting the development of state-of-the-art gene-based
therapies for ultrarare neurological diseases, which affect as few or fewer than one in fifty thousand people.

In ASGCT’s letter to FDA regarding Reauthorization of the Prescription Drug User Fee Act (PDUFA), the Society suggested that FDA develop a collaborative public/private partnership with researchers, industry, and other key stakeholders with the specific purpose of addressing crucial issues and barriers in gene and cell therapy development. We appreciate that NCATS is soliciting information on existing public/private partnerships in the space, to assess the need for this potential solution.

*Can a system that provides for a few patients transition to a system that is comprehensive without becoming insolvent?*

Because the current predominant model of commercial development includes expectations of return on private investment, most biotechnology and pharmaceutical companies need to focus on therapies for genetic disorders with sufficient commercial potential. Therefore, gene therapies for ultrarare diseases are not often able to be developed through this mechanism. To begin to address this issue, on June 22, ASGCT hosted a virtual *Forum on Gene Therapy for Underserved Populations: Drug Development for Ultrarare Diseases and Lower-Income Countries*. Speakers at this event, which was free and open to the public, addressed approaches to creating alternative sustainable business models for development. These included the Bespoke Gene Therapy Consortium (a public-private partnership) and several speakers on non-profit biotechnology models. In addition, the program included speakers addressing the following: NCATS’ platform approach to streamlining development; efficient manufacturing; open access and data sharing; and patient foundation-led development. Each of these topics highlight elements needed to facilitate development for a greater number of rare diseases.

The Society advocates for policies for public payer coverage and reimbursement that best facilitates patient access to gene therapy and distributes risk fairly among payers and developers, while supporting adequate reimbursement of providers to allow them to offer approved therapies to public payer beneficiaries. More details on our positions on payment policies are described below.

**What methods should we use to communicate with patients and families regarding gene-targeted therapies?**

ASGCT has a [Patient Education Program](#), initiated in 2019, that has been successful in communicating with patients and families regarding gene therapies. As treatments for more diseases enter the clinical pipeline, additional resources may be beneficial to enable more rapid expansion of this content and to facilitate greater distribution of this information to those in need of it.

The Society’s processes exemplify methods that should continue to be used for multi-stakeholder collaboration on accurate, accessible educational content. A needs assessment identified a clear gap in dynamic gene therapy educational content for a lay audience that ASGCT is well positioned to address through the expertise of its members. Our Patient
Outreach Committee, composed primarily of scientific and clinical experts in the field (plus patient advocate representatives), reviews content for accuracy. Our Patient Education Program currently consists of 29 gene and cell therapy resource units with animated video, infographics, and written content on general and disease-specific topics related to gene therapy. The Society creates additional units annually. Disease-specific topics are selected by the Patient Outreach Committee based on input on educational need from patient advocacy groups, as well as the amount and phase of clinical development for each prospective topic.

In addition to leveraging ASGCT member expertise, a key aspect of the Patient Education Program is connecting throughout the resource production process with patient advocacy organizations who are impacted by the diseases being covered. We have collaborated with approximately 50 different groups to date on patient-focused programming. Through collaborative relationships with patient advocacy organizations, ASGCT identifies patient and parent educational needs on each topic, obtains feedback on content during creation; and shares completed units with organizations that are willing to distribute the materials to their patient constituencies, through means including embedding the videos on their own websites and sharing via social media.

The success of this approach is evidenced by the following usage metrics:

- 300,000+ YouTube views of 23 patient education videos since resources were initially launched in January 2019
- 8,107 clinical trials video views
- 63,390 visits to the Patient Education website in the six months after October 1, 2020, the date all resources were transferred to their own dedicated site
- Visitors spend an average of ~3 – 4 minutes on Patient Education Program web pages (industry standard is 2 – 3 minutes)

Anecdotal feedback regarding the patient education program from patients, advocates, and clinicians gathered through focus groups conducted in December 2020, includes:

- “Every organization or group doing something with gene therapy should have your information or videos on their website, because it is so streamlined and so easy to understand.”
- “This does a good job of meeting the patient where they are.”
- “I have referred a number of patients and organizations to this material with really positive responses.”

ASGCT would welcome opportunities to expand dissemination channels to patient and family populations for this information. Our resources are free to share, and we encourage open access for their utilization. ASGCT collaboration with additional stakeholders is an area of opportunity for furthering communication with patients and families.

The Society also hosts a clinical trials finder that exclusively contains gene and cell therapy trials (including RNA therapies). This finder compiles clinical trials from clinicaltrials.gov, improving upon the ability to search for gene and cell therapy clinical trials, which are curated daily and vetted using ASGCT parameters to exclude non-interventional trials and trials that are
not deemed gene and cell therapies. In addition, the finder allows patients or families to use the filters to search by diagnosis, geographical location, modality, and trial status.

3. Consider the methods that will ensure equitable access to gene-targeted therapies

How can we address potential disparities in access to these therapies?

Current federally financed coverage and reimbursement mechanisms for new medical products are outdated in their ability to accommodate those gene and cell therapies that consist of a one-time biologic product, plus services to provide the therapy. With more than 60 durable cell and gene therapies likely to be approved in the US by 2030, it is critical these mechanisms are reformed to keep pace with innovation.

To this end, the Center for Medicare and Medicaid Services (CMS) has finalized regulation that will enable value-based, risk-sharing arrangements that tie payment to product performance. (CMS is proposing delaying implementation of this provision of the rule by six months—to July 1, 2022—to allow adequate time to operationalize the changes.) ASGCT supports this concept as such arrangements could provide cost savings to patients and payers, including state Medicaid programs. In addition, doing so redistributes some risk of uncertain outcomes from payers to manufacturers and distributes costs more equitably based on individual patient outcomes. In addition, ASGCT supports allowing for VBP arrangements that include a pay-over-time component. Enabling payment models that combine the two concepts would be useful by, for example, allowing payers to make installment payments upon patient attainment of benchmarks of efficacy. Doing so ties a portion of product value to durability over time.

Because gene therapies demonstrate a potential for substantial improvement over available therapies or the potential to become the first and only available therapy for serious or life-threatening conditions, expedient development is imperative and often leads to limited clinical trial populations to develop the evidence needed to support labeled indications. The potential for limited clinical trial populations is warranted to make transformative treatments available to patients quickly but can cause payer misconceptions that after approval, only patients that meet the clinical trial criteria should be covered, rather than covering to the FDA label. Under Medicaid and some private payers, known problems exist with failing to cover therapies to FDA-labeled indications; in the case of Medicaid, these problems occur despite a federal requirement to cover to label.

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3 ASGCT payment policy positions do not imply endorsement of any individual pricing decisions.


6 As a scientific research association, ASGCT recognizes the challenges of identifying appropriate outcome measures for use as indicators of treatment success. We offer the scientific expertise of our membership as a resource to you and to CMS in assessing the appropriateness of proposed outcomes measures within value-based purchasing arrangements.
To demonstrate this issue, for CAR T-cell therapy, some state Medicaid healthcare plan coverage criteria are more expansive than the FDA label indication statements for both Yescarta and Kymriah. Of the 24 states that had coverage policies at the time of a study of this topic, there were 20 different health care plan coverage criteria for Kymriah for ALL. Seventy-five percent of the health care plan coverage criteria for the ALL indication were associated with the inclusion/exclusion criteria for the registrational trial. Nearly half of states have site-of-care coverage restrictions (some for inpatient and some for outpatient administration). Barriers to Medicaid access are especially concerning for patients with potentially fatal and/or progressive diseases, for which early administration of a therapy may prevent morbidities and mortality, and in some cases potentially reverse morbidities. State program denial of coverage for therapies for non-medical reasons is not appropriate. Enforcement of the requirement for Medicaid programs to cover gene therapies to the FDA-labeled indications would be a significant step to ensuring equitable access. Medicaid programs’ discriminatory coverage practices may lead to disparities as commercially covered individuals might disproportionately obtain access more easily. We recommend that products with FDA’s Regenerative Medicine Advanced Therapy and Breakthrough Therapy designations be considered medically necessary if prescribed by the provider; not as determined by the payer.

We further recommend greater coordination between CMS and FDA regarding the confirmatory evidence needed to fulfill post-marketing obligations and demonstrate effectiveness. These measures would allow for expedited coverage with subsequent collection of evidence through mechanisms that are already in place. However, it is important to differentiate concepts of market-readiness from regulatory approval. FDA’s remit should remain focused on ensuring safety and efficacy without delving into pricing and access concerns to ensure the integrity of regulatory review and assessments is preserved. The Society encourages consideration of additional ways for CMS to provide a more streamlined, consistent approach to providing immediate and uninterrupted coverage for these potentially lifesaving treatments.

In addition to payment policy solutions to increase equitable access to gene therapies, methods should be implemented to increase minority participation in clinical trials, which is disproportionate to representation in the population. Studies show minority groups are as willing to participate as Whites in clinical trials, but are less likely to be invited to participate. The disparity in trial participation is also due to lack of access to medical treatment due to logistical barriers (such as lack of transportation/financial burden, interference with work/family responsibilities, and out-of-pocket expenses), and being less likely to be offered trial information.


One solution to this problem is to increase the awareness of clinical trials among patients and their families. Because minorities are less likely to be offered information about clinical trials, provision of educational materials on clinical trials in general, and on gene therapies in particular, need to be fit to the audience and distributed in ways that will reach minority audiences.

For those who are not willing to participate in trials, mistrust of research is another factor limiting trial participation. Key to improved recruitment would be recruitment by familiar and credible individuals, such as community service centers and community health centers. Important to equitable access to clinical trials will be increasing the distribution of patient education content on clinical trials for gene therapies and on gene therapy for rare diseases that disproportionately affect minorities, such as sickle cell disease. ASGCT is interested in partnering with other stakeholders in adapting and distributing our patient education materials to minority patients and families on clinical trials and gene therapy for sickle cell disease.

**What can be done to encourage collaboration and increased communication among various stakeholders?**

ASGCT has encouraged communication among various stakeholders by convening them in educational programming at our Annual Meeting and Policy Summit each year. Continuing to do so is one way to facilitate ongoing multi-stakeholder engagement on equitable access to gene therapies. To demonstrate future possibilities, examples of programming include: a patient-facing workshop to increase connections between researchers and patients to facilitate patient group-led development; a session to address insights on development and access to gene therapies globally; multiple sessions on newborn screening policy; and workshops and sessions on regulatory policy, including convening global regulators to provide additional perspectives on best practices for development from a regulatory perspective.

As mentioned previously, we convened speakers on June 22 on a variety of approaches to enhance development of gene therapies for individuals with ultrarare diseases and from countries with lower-income economies. Additionally, the Society has had a variety of stakeholders speak about payment policy for gene therapies; a recent example is a workshop on patient and market access that included speakers from a biotechnology company; payers; investors; legislative staff; and a parent of a patient who experienced challenges in obtaining commercial insurance coverage for the gene therapy for spinal muscular atrophy (SMA). ASGCT would be pleased to continue to lead and/or assist in this role as a convener of various stakeholders, both in future educational programming and in facilitating smaller group discussions on solutions to enhancing equitable development and access.

**What types of innovations are needed to enable and support development of gene therapies in a timely fashion?**

Responsibility for the timely development of safe and effective gene therapies rests within the productive working relationship between product sponsors and the Food and Drug

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Administration. To that end, we provide several of our top regulatory priorities based on feedback from both industry and academic members.

ASGCT encourages FDA to allocate additional appropriations and user fee dollars to support the Center for Biologics Evaluation and Research (CBER) to “right size” support compared to the volume and complexity of new products. CBER has over 1,000 active investigational new drug applications supporting clinical research on the transformative therapies of the future. ASGCT members report that many meeting requests for pre-IND and PDUFA meetings, and even engagement during reviews, have been significantly delayed both before and during the pandemic. These engagements are critical to the development process to ensure product sponsors are pursuing development strategies that will meet FDA’s critical safety and efficacy standards. Additional communications strategies should also be considered, given the rapid pace of development, such as optional communication plans which have shown success in the Center for Drug Evaluation and Research (CDER) to identify the most appropriate times for meetings, the type of data to be discussed at each landmark, and to reduce unforeseen regulatory hurdles.

ASGCT also supports FDA’s efforts to produce guidance for industry documents to help clarify development challenges for gene therapies. When developed and implemented, these guidance documents can be extremely helpful for both industry and academic members of ASGCT in clarifying regulatory pathways and decreasing uncertainty. While intended for an industry audience, academic researchers embarking on basic, translational, and early-phase clinical research projects also benefit from understanding how FDA views clinical development issues, the types of data FDA requires, and the areas of regulatory uncertainty, to most efficiently and effectively use scarce research dollars to answer questions that will contribute to expeditious advancement of the field for patients.

ASGCT recommends that FDA provide greater clarity regarding expectations for the manufacturing and Chemistry, Manufacturing, and Controls (CMC) data that will be required at various stages of development, application submission, and post-market settings. Unlike traditional drug products, gene therapy product manufacturing often develops in parallel with clinical development; product sponsors can make changes to improve yield and efficacy based on early clinical findings. In this respect, final CMC data often comes later in the product life cycle. We recommend that FDA take these differences into consideration in further guidance, which should also address when in the development program sponsors should engage with FDA regarding CMC data and how communications should continue through approval to ensure clear benchmarks.

As was discussed above, greater coordination between FDA and CMS is critical. Post-market surveillance ensures that approved products remain safe and effective. As more gene therapies are approved by FDA that require further post-market assessment, it is critical these assessments are designed to answer the scientific questions at hand, be practical to effectuate in the market, and not impede patient access. Studies designed with greater consideration of practical barriers and market-based questions will be more likely to accrue and retain patients, giving the Agency and product sponsors more rapid and complete information about the performance of products on the market.
Thank you for your consideration of these comments. Please let us know if you have questions by contacting Betsy Foss-Campbell, Director of Policy and Advocacy, at bfoss@asgct.org.

Sincerely,

Beverly Davidson, PhD
President
American Society of Gene & Cell Therapy