June 30, 2021

National Center for Advancing Translational Sciences
6701 Democracy Boulevard
Bethesda MD 20892-4874

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 Sir or Madam,

In service of the neuromuscular disease (NMD) patient community, we thank the National Center for Advancing Translational Sciences (NCATS or "the Center") for the opportunity to comment on the Request for Information (RFI) entitled, "Facilitating the Early Diagnosis and Equitable Delivery of Gene-Targeted Therapies to Individuals with Rare Diseases". We are grateful for the Center's continued dedication to facilitating development of, and access to, gene therapies for those with rare diseases, including the neuromuscular disease community.

At MDA we are focusing intensely on understanding the genetic and molecular origins of neuromuscular diseases to advance genetic diagnoses and to support the development of disease therapies — including antisense oligonucleotides and gene-replacement and gene-editing therapies — that target the underlying genetic cause. From the beginning MDA has contributed greatly to the field of muscle disease and toward landmark research advances, including the identification of the first human disease-causing gene as well as the first human trial of gene transfer for a muscle disease.

For several decades, MDA-supported researchers have discovered the gene-causing mutations for many other neuromuscular disorders, developed and refined gene delivery tools and methods, and funded innovative research looking for other creative ways to circumvent the problems created by genetic defects. Indeed, recent FDA approvals for gene-targeted therapies for neuromuscular diseases, as well as even more experimental therapies currently in advanced clinical trials, are the result of decades of effort from a large community of partners, including families, donors, researchers, and clinicians.

Simply put, gene therapies for neuromuscular diseases represent the future paradigm of treatments for the neuromuscular disease community. Consequently, we are grateful for the opportunity to provide comments to NCATS on the development and equitable delivery of gene-targeted therapies.

1. ***To develop infrastructure for the efficient, effective, and equitable distribution of therapies it is important to define the following:***
   - *Consider who are the individuals that could benefit from gene-targeted therapies – now and in the future.*

- *Consider what rare diseases or categories of rare diseases are most amenable to gene-targeted therapies – now and in the future.*

For now, the most immediately amenable diseases to gene therapy are monogenetic autosomal recessive disorders for which delivering a healthy copy of the affected gene should restore function. In particular, diseases that are not irreversibly degenerative will likely have the best outcome. Additionally, diseases that are caused by a lack of a secreted protein that can be manufactured in a variety of tissues other than, or in addition to, the tissues that are the native source of the protein hold particular promise for gene therapy development. Further criteria that make certain diseases more amenable to gene therapy development are conditions that do not have narrow safety windows for gene dosage and diseases for which the therapeutic gene will fit into an AAV capsid (as the most commonly used type of viral vector).

An example of a disease category that fits all of the above criteria is hemophilia, but many of the neuromuscular disorders on which MDA dedicates our research efforts also fit the majority of these categories, such as X-linked myotubular myopathy. In the future, if we are able to better regulate expression of genes delivered via gene therapy, then we can also prioritize disorders for which gene dosage is very critical (i.e., Rhett syndrome). So, while some diseases and disease areas are more amenable that others with our current technologies to gene-targeted therapies, we aim for all neuromuscular diseases caused by genetic variants to one day be amenable to gene-targeted therapies.

- *Consider when is the optimal time to identify individuals who could benefit from gene-targeted therapies (e.g., newborn screening)*

Individuals who have degenerative disorders, like the muscular dystrophies, spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS), and other neuromuscular disorders will almost always benefit from earlier treatment as it is easier to prevent disease than reverse it. In the case of many of these disorders you cannot add genes back to cells that have been lost already.

In the case of neurological diseases, nerve cells often cannot be regenerated, and in the case of muscle diseases, scarring and fibrosis may represent additional barriers to treatment. Upon FDA approval of the first safe and effective intervention that, if administered early, can prevent further degeneration, MDA is supportive of rapid inclusion of the disease on the Secretary's Recommended Uniform Screening Panel (RUSP). Upon inclusion on the RUSP, MDA urges states to add the screen to their panels as soon as possible. Unfortunately, the current process is very long and convoluted and can often take years following FDA-approval of therapy for all states to adopt the recommended screen. This delay may be costing the wellbeing of many individuals with these degenerative diseases because they were diagnosed only after the disease irreversibly progress.

Nonetheless, newborn screening (albeit ideally a newborn screening system that moves much more rapidly than our current approach) holds the greatest promise for diagnosing individuals who could benefit from gene-targeted therapies as early as possible.

Individuals with neuromuscular degenerative disorders who have already experienced loss of affected tissues and function may still benefit from gene therapy if the therapy can arrest the progress of the disease. Many people with degenerative diseases have indicated that constantly adjusting to new levels of loss is one of the hardest aspects of living with the disease as it is difficult to plan for constantly decreasing levels of functionality.[1] Furthermore, decreasing functionality impacts ongoing medical and equipment needs, straining an already overloaded healthcare system where it can take 6-12 months to receive approvals for new equipment, just in time to need something different. This coverage and access process is unnecessarily burdensome not only on individuals with neuromuscular diseases and their loved ones, but also on clinicians and other medical professionals providing care for an individual with degenerating functionality. So earlier is better, but later is still very worthwhile.

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:***
    - *Consider the current mechanisms for diagnosing and identifying individuals with rare diseases for gene-targeted therapies.*

Individuals with rare neuromuscular disease are currently diagnosed in a number of different settings, but many individuals with an NMD report that the diagnostic journey can be quite long. For example, in neuromuscular disease, there is usually a history of misdiagnoses and multiple specialists seen before a referral to a neuromuscular specialist is made. If a disease "runs in the family," usually because it is inherited in a dominant fashion, families may be proactive in screening for carrier status or in obtaining genetic testing if a sibling is affected.

Barriers to genetic testing, which is usually needed for subsequent access to a gene-targeted therapy, remain prevalent. Coverage in both private and public health insurance plans often limit access to genetic tests making it difficult to confirm genetic diagnosis of the disease in question. Consequently, in order to facilitate wider-spread access to gene-targeted therapies, it may be necessary to also address the barriers to accessing genetic testing.

Finally, a genetic test is often only as good as the geneticist who can interpret it. Unfortunately, with a shortage of geneticists, obtaining accurate and actionable results from a genetic test can be challenging.[2] During the pandemic, telehealth rules and restrictions have been loosened to allow medical professionals to practice across state lines. This has been particularly beneficial to addressing the geneticist shortage as geneticists can care for individuals with neuromuscular diseases, including in interpreting the results of genetic tests, far from their clinic or practice. Consequently, in addressing the infrastructure needed to disseminate gene-targeted therapies, barriers to telehealth that may resume as the pandemic wanes need to be addressed.

[1] For examples of patient testimonials on the constant difficulty of dealing with further progression of their neuromuscular disease, please see the variety of "Voice of the Patient Reports" published following Patient-Focused Drug Development meetings, including those for SMA, Charcot-Marie Tooth, Friedreich's Ataxia, Facioscapulohumeral muscular dystrophy (FSHD), and more.

[2] Jenkins, B. D., Fischer, C. G., Polito, C. A., Maiese, D. R., Keehn, A. S., Lyon, M., Edick, M. J., Taylor, M., Andersson, H. C., Bodurtha, J. N., Blitzer, M. G., Muenke, M., & Watson, M. S. (2021). The 2019 US medical genetics workforce: a focus on clinical genetics. Genetics in medicine: official journal of the American College of Medical Genetics, 1–7. Advance online publication. https://doi.org/10.1038/s41436-021-01162-5

- *Consider how can the early diagnostic process be improved; Consider other models that can be developed and used to better identify individuals who can benefit from rare disease therapies in a timely manner.*

As our ability to sequence whole genomes improves there are likely more expedient ways to diagnose rare genetic disease. Even now, commercial enterprises like 23&Me screen for several rare and common genetic defects, but these are generally requested and paid for by curious consumers with the means to do so. Nonetheless, as genetic testing becomes more widely available and accessible, it is worth exploring what can be learned from these direct-to-consumer tests.

Newborn screening is also evolving in the direction to potentially including genetic testing at birth for "actionable" genetic variants. While we are still in the nascent phases of testing these approaches, it is worth investing further in what genetic testing at birth could look like for a future paradigm.

- *Consider the current means of communicating information related to gene-targeted therapies to primary care physicians and other healthcare providers.*

Currently, much of the information on gene-targeted treatments provided to healthcare providers is produced by the biopharmaceutical companies that develop and subsequently manufacture the treatment as well as patient advocacy organizations. Nonetheless, information on gene-targeted treatments is very inconsistently offered to the broader primary care physician and clinical population. Current education efforts usually focus on those specialists that routinely treat patients with the genetic disease in question.

Ideally for primary care physicians (PCPs), focus on disease awareness, the urgency of early recognition and diagnosis, and the importance of referring the patient a specialist who can administer gene-targeted therapies is critical. Professional organizations and patient advocacy groups conduct annual conferences and medical education programs that could be the ideal method not only for specialist training, but for disease awareness for the broader clinical community. These organizations generally provide continuing medical education (CME) credits, important for medical professionals of all types. Additionally, published literature needs to address the practical implementation and treatment requirements for clinicians. Currently there is limited literature and medical education programming focusing on the clinical implementation and clinical care associated with gene-targeted therapies.

In summary, a multimodal strategy involving a variety of educational offerings (conferences, webinars, roundtables, whitepapers, academic publications, trade publications, grand rounds, etc…) is likely needed. Such multimodal efforts must not be limited to the prescribing physician, but instead must include the full multidisciplinary team. Afterall, although the treatment may just be an IV infusion, the logistics of rapidly obtaining, infusing, and monitoring an individual receiving [a gene-targeted therapy] requires a coordinated care center experienced with caring for individuals with serious genetic diseases.

- *Consider methods we should use to communicate with healthcare providers, patients, and families regarding gene-targeted therapies and list and/or describe.*

As discussed previously, communicating the risks and benefits associated with gene-targeted therapies needs to be multimodal and tailored to the intended audience. For example, for patients concerned about the long-term effects a gene-targeted therapy may have on them, evidence-based education in laymen terms on the long-term risks of gene-targeted therapies should be crafted in partnership with patient advocacy organizations and healthcare providers who may be delivering such information.

This is just one example of the variety of educational efforts that must be collaborative across the relevant stakeholders for any given gene-targeted therapy.

3. ***Consider the methods that will ensure equitable access to gene-targeted therapies.***
   - *Consider how can we address potential disparities in access to these therapies.*

There are a variety of barriers to equitable access to gene-targeted therapies that need to be addressed. First, there are many individuals with rare diseases who may benefit from gene-targeted therapies that are simply not reached by the stakeholder community, and consequently may not know the opportunities in front of them. This may be due to any number of reasons, but often may be due to socioeconomic and/or systemic cultural and racial barriers to accessing quality information, assistance, and care. It is incumbent, and long overdue, on the stakeholder community (and in particular patient advocacy organizations, biopharmaceutical companies, the research community, and governmental entities) to reach the communities that have been left behind. MDA welcomes and calls for conversations and subsequent initiatives that target the systemic racial and cultural biases that have prevented the stakeholder community from adequately serving minority and underserved communities in the United States.

Similarly, language barriers can present challenges for non-English and English-as-a-second language (ESL) speakers. The information required to truly understand the benefits and risks of gene-targeted therapies is complex enough without adding language barriers to further challenge the situation. Translation services must be utilized widely for any initiative attempting to better prepare the rare disease community and general public for gene-targeted therapies.

Access and affordability challenges continue to adversely affect many in the rare disease community. The cost of care and health insurance continues to be unaffordable for many, and additional insurance barriers of narrow networks, formulary exclusions, adverse benefit designs, and high cost-sharing often put specialists and targeted therapies out of reach. Consequently, to prepare for wider access to gene-targeted therapies, public and private health insurance coverage must prepare for the anticipated high-cost of these therapies.

One such preparation should include further consideration of methods to amortize payments for gene therapies over time to lower the one-time cost of a single-use therapy. These amortized payments should be tied to continuing effectiveness of the treatment and ideally be portable across insurers.

Finally, transportation barriers can prevent individuals in the rare disease community, particularly those without the privilege to miss employment or other responsibilities, from traveling to specialty clinics to receive the specialty care before, during, and after the administration of a gene-targeted therapy. Transportation is also particularly difficult for those with mobility challenges. A recent survey from MDA found that of those in the neuromuscular disease community who did not participate in clinical trials, over twenty percent of respondents cited transportation barriers as the reason for not participating.[3] We have no expectation that these challenges would be lessened for those seeking gene-targeted treatments.

While many additional barriers exist for equitable access to gene-targeted therapies, existing systemic inequities, cost and access barriers, and transportation challenges are three of the most challenging barriers to overcome.

- *Consider what can be done to encourage collaboration and increased communication among various stakeholders.*

One of the most important aspects of cross-stakeholder collaboration will be unified messaging on the benefits and risks of gene-targeted therapies. We need to be sure patient advocacy organizations, the biopharmaceutical industry, governmental authorities, and all other stakeholders are unified in delivering the same fact-based information to the rare disease community. Consequently, such partnerships should be developed as soon as possible to prepare for the future wider availability of gene-targeted therapies.

Further encouragement and pressure from governmental regulators, such as the FDA, on the biopharmaceutical industry to not create redundant clinical trial networks, centers of excellence, and natural history data registries to capture gene-targeted therapy long-term follow up data will be integral to encouraging collaboration. Otherwise, the continued practice of each biopharmaceutical company setting their own network, centers of excellence, and long-term follow up process will create entirely avoidable redundancy and siloes.

- *Consider what currently facilitates provision of, or inversely limits access to targeted therapies for patients with rare diseases and list and/or describe.*

To start, specialty centers with experience in administering therapies, monitoring for adverse events, and applying for reimbursement currently facilitate the provision of gene-targeted therapies. Patient advocacy organizations are also facilitators as they can help educate patients and physicians about gene therapy. Commercial companies such as 23&Me, Invitae, and other diagnostic developers may be able to contribute to earlier diagnoses. Finally, a facilitator that is too often underutilized are burden of disease studies that establish societal costs of not treating genetic diseases, and consequently strengthen the argument for societal and governmental investment in development and dissemination of gene-targeted therapies.

[3] ONEVoice: Insights and Observations from a National Survey of Adults and Families Living with Neuromuscular Disease (2018, December 9). Retrieved August 1, 2019, from https://www.mda.org/sites/default/files/2018/12/MDA_OneVoice_Whitepaper.pdf.

Simultaneously, there are many limitations to consider. As discussed above, a diagnosis of the underlying genetic variant amenable to a gene-targeted therapy is needed, but not always accessible. Continuing misunderstandings on the safety of gene therapies still permeate the impression many have of gene therapies, consequently skewing the risk/benefit analysis individuals may undertake. Many in the rare disease community understand that receiving a gene-targeted therapy many limit their eligibility to participate in other clinical trials or prevent them from receiving other current or future treatment options, including the next generation of gene-targeted therapies.

Additional limitations include those already discussed pertaining to lack of understanding and ability in the non-specialist clinical community as well as the bandwidth needed of clinics and medical professionals to navigate the administration, follow-up, coverage, and reimbursement aspects of administering a gene-targeted therapy. Travel limitations remain for many in the rare disease community either due to socioeconomic factors or mobility issues.

Finally, financial and economic barriers remain for the development of gene-targeted therapies. The commercial pathway for treatments for incredibly rare diseases remains unviable leaving many potentially safe and effective treatments going undeveloped by the biopharmaceutical industry. Additionally, also as mentioned above, the paradigm of covering and paying for gene-targeted therapies needs to shift towards amortized value-based portable payments.

This is certainly not an exhaustive list of the facilitators and limitations to accessing gene-targeted therapies, and MDA welcomes to opportunity to discuss these and all the other existing elements to accessing gene-targeted treatments.

- *Consider what type of innovations are needed to enable and support development of gene-targeted therapies in a timely fashion.*

While many innovations are needed, MDA believes advocacy organizations can play a prominent role in accelerating the effort to develop and deliver gene-targeted therapies. First, advocacy groups may be able to play a role in facilitating more equitable access to therapies by arranging transportation, “hub and spoke” care models to reach rural areas, and other targeted programs. Advocacy organizations can work with governmental bodies and medical societies to develop better educational materials for clinicians.

In conclusion, we are grateful for the opportunity to comment on this RFI on equitable gene-targeted therapy development and delivery. For questions regarding MDA or the above comments, please contact me at 202-253-2980 or pmelmeyer@mdausa.org.

Sincerely,

Paul Melmeyer, MPP
Vice President, Public Policy and Advocacy