Joni Rutter, Ph.D.,
Acting Director
National Center for Advancing Translational Science (NCATS)
National Institutes of Health
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 Dr. Rutter,

We, the undersigned patient voluntary organizations, collectively represent the 3.4 million Americans and 65 million people worldwide living with the epilepsies. Our organizations support families, drive research agendas, champion disability rights, and provide education and awareness. We envision a future in which every person with epilepsy has access to precision treatments that go beyond controlling seizures but can instead modify the underlying disease processes, or prevent epilepsy itself, while living their highest possible quality of life.
We commend the NCATS for requesting public input on this topic. We are pleased to comment on the following areas related to the effective, efficient and equitable distribution 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*
   - *Consider **when is the optimal time to identify individuals** who could benefit from gene-targeted therapies (e.g., newborn screening)*

Epilepsy is a collective term for the epilepsies; a diverse spectrum of seizure-related disorders that result from many different causes across the lifespan[1]. Gene targeted therapies may be useful at different stages of life depending on the etiology of the epilepsy. There are near-term and longer-term opportunities for gene-targeted therapies in the epilepsies.

It is estimated that 70-80 % of epilepsies are caused by genetic factors, either by single gene variants, polygenic interactions, somatic mutations, and/or epigenetic changes that can present within the first decade of life[2],[3]. Near term, gene-targeted therapies may be most relevant for monogenic epilepsies or epilepsies that converge on a common biological pathway.

Longer-term gene-targeted therapy development opportunities also exist. Acquired epilepsies such as from traumatic brain injury or epigenetic changes can lead to "acquired channelopathy" causing epilepsy[4]. This results in a large proportion of people with epilepsy who could potentially benefit from gene-targeted therapies of various types even where the initial cause is not genetic[5]. Additional knowledge generated from basic research is needed to advance the understanding of the genetic underpinnings of acquired epilepsies.

For many of the epilepsies, the ideal timeframe for identification is not known and there is likely a delay of months to years in making a diagnosis for patients with early onset seizures[6]. However, in many instances of genetically based epilepsies, the conditions can be progressive and the earliest possible intervention could improve outcomes. Examples of conditions in which identification at or before birth is most likely to lead to better outcomes includes Tuberous Sclerosis Complex (TSC), infantile spasms associated with a known gene mutation, Dravet syndrome, Angelman syndrome, or specific variants in SLCA35 and SLC6a1, to name just a few. See for others https://doi.org/10.1016/j.seizure.2016.11.030 for others.

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*

There is no single diagnostic tool to diagnose rare epilepsies. Many patients rely on a combination of clinical evaluation; family history, prior medical history, seizure semiology, age of onset, existence of co-occurring conditions (such as developmental delays), electroencephalogram (EEG) monitoring, genetic and molecular testing such as defined epilepsy gene panels, whole exome and whole genome sequencing, metabolic panels, and neuroimaging. In a landscape analysis of Rare Epilepsies[7], the following diseases reported diagnosis was validated by genetic and or molecular testing: GRIN2B, GNAO1, GAT1, KIF1A, Ring Chromosome 20, SCN2A, STK9, CDKL5, Chromosome 8p, SCN8A, WDR45/WIPI4, 22q Deletion, Shank3 mutation, CLN1, CLN2, CLN3, CLN4, CLN5, CLN6, CLN7, CLN8, CLN10, CLN11, CLN12, CLN13, CLN14, SYNGAP1, Ring 22, SLC13A5, DNM1, SLC9A6, TBC1D24, SYNGAP1, and TBCK. Additionally, referrals from other specialties like psychiatry, GI, cardiology, endocrinology, dermatology and pulmonology may lead to a rare epilepsy diagnosis. Many patients ultimately diagnosed with a rare epilepsy may experience a diagnostic odyssey where their diagnosis is missed, they are misdiagnosed, or an accurate diagnosis is delayed by months, years and sometimes even decades [8]. This patchwork of non-standardized diagnostic pathways is not ideal and may slow down or prevent the identification of individuals most eligible for life changing interventions.

- *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*

A more efficient mechanism for diagnosing and identifying individuals with rare epilepsies for gene-targeted therapies would require 1) standardized diagnostic pathways that also reliably include genetic evaluation at an appropriately early stage, 2) enhanced education of providers and payers about the clinical utility of genetic evaluation within the diagnostic process, 3) community-consensus that high-quality epilepsy care depends on diagnosis of precise etiology in addition to seizure types and/or syndromes, and 4) standardized diagnostic nomenclature included in searchable fields in the electronic medical record.

On point 3) above, we celebrate that professional society partners like the Child Neurology Society have included a similar recommendation in their response to this RFI. In addition, the key accreditation organization for epilepsy centers, the National Association of Epilepsy Centers (NAEC) has announced a process to revise practice guidelines over the next 18 months[9] to bring the accreditation standards up-to-date with current state of the art. This NAEC-led activity presents an opportunity to develop a community consensus around the current and future value of genetic evaluation in epilepsy care.

With regard to point 4), although some rare epilepsies have been included in the International Classification of Disease (ICD) system in the ICD-9/10 versions, many more have not. Computable phenotypes have been developed to identify those with rare epilepsies from terms in standardized vocabularies[10], but these are not yet in widespread use to identify individuals with rare epilepsies.

- *Consider what other methods/platforms to identify such individuals that could be leveraged and list and/or describe.*

Early Diagnosis can be improved now and in the future by:

- Near-term: Sequencing after 1st unprovoked seizure. Further, broaden education of practitioners from ERs, internists, pediatricians, neurologists as well as other adjacent specialties about refractory epilepsy to expedite sequencing and gene –targeted interventions.
- Future: Routine utilization and expansion of newborn screening and identification of epilepsy-associated predictive biomarkers.

New models that incentivize collaboration across multiple stakeholders, for example Invitae's Behind the Seizures program[11] that enables genetic diagnosis and expanded understanding the genetic causes of epilepsy, are required. The Behind the Seizures program is a collaboration between a genetic testing company and multiple pharmaceutical companies that are developing treatments for rare epilepsies.

In addition, at least two **Learning Health Networks** (LHN) that use standardized diagnostic terms have been established in epilepsy. In each of these LHNs, standardized data from epilepsy patients seen in the system are aggregated into a registry that could enable rapid identification of rare epilepsy patients. One, the Pediatric Epilepsy Learning Health System[12] (PELHS) is hosted by the Pediatric Epilepsy Research Consortium[13] (PERC) with membership drawn from PERC centers (large academic medical centers serving pediatric patients and their families). The other, the Epilepsy Learning Healthcare System[14] (ELHS) is a Healthier Together[15] LHN hosted by the Epilepsy Foundation on behalf of a multi-stakeholder group including NAEC-accredited epilepsy centers at pediatric and adult academic medical centers, patients and their families, social services organizations, rare epilepsy organizations, and others. Currently, PELHS and ELHS both have fewer than 20 participating centers. Expanding the participation of epilepsy centers and those neurology practices that see patients i with epilepsy n these LHNs would expand the capacity to rapidly and accurately identify patients with rare epilepsies.

- *Consider if there are currently any public/private partnerships in existence that support gene-targeted therapies and list and/or describe.*
- *Consider if a system that provides for a few patients can transition to a system that is comprehensive without becoming insolvent*

Existing **newborn screening** currently aids in identification of some known rare epilepsies due to metabolic disorders. After infants or children display seizures, epilepsy gene panels are available through a number of diagnostic laboratories for diagnosis of ~100 gene variants that are associated with disease. However, genetic testing is not always covered by payers, creating a barrier for many individuals and families. In particular, there is serious risk of exacerbating **existing health disparities** in epilepsy experienced by people of color, those with lower socioeconomic status, and geographic locations, among others, if access to insurance continues to be a determining factor in whether a patient receives genetic testing.

In addition, the use of genetic testing for resistant epilepsy in adults has lagged far behind its use in infants and children. In part, this is due to 1) lack of familiarity and understanding of the genetic landscape of the epilepsies among adult epilepsy providers, and 2) a sense that confirmatory genetic results would not alter treatment decisions by adult providers, in addition to the coverage barriers.

However, there are already several examples specific to epilepsy where information about a precise genetic diagnosis can change the course of a disease and outcomes[16]. For example, anti-seizure medication is usually the first line of therapy, and other treatment modalities like surgery or ketogenic dietary therapy are not considered until a patient's seizures have failed to be controlled by adequate doses of at least two anti-seizure medications. If the epilepsy is caused by a specific metabolic defect in glucose processing, GLUT1 deficiency, however, the ketogenic diet is an appropriate first line therapy. Additional examples exist when epilepsy is caused by certain

gene variants in sodium channels, including pathogenic SCN1A or SCN8A variants. Such variants should direct a provider away from using any of the sodium channel blocking drugs as the anti-seizure medication of choice. If given, these drugs will exacerbate seizures in these selected patients. Everolimus, an mTOR inhibitor approved for the treatment of focal seizures associated with tuberous sclerosis complex, is an example of a medication targeting the etiological mechanisms of the disease. Several treatments aimed at correcting specific pathogenic defects responsible for rare genetic epilepsies are currently in development, and range from traditional small molecules to novel approaches involving peptides, antisense oligonucleotides, and gene therapy.

- *Consider the current means of communicating information related to gene-targeted therapies to primary care physicians and other healthcare providers*
- *Consider methods we should use to communicate with healthcare providers, patients, and families regarding gene-targeted therapies and list and/or describe*

The Project ECHO[17] (Extension for Community Health Outcomes) model may be an excellent approach to consider for communicating with primary care physicians and other healthcare providers about gene-targeted therapies. The collaboration agreement for Project ECHO states "The mission of Project ECHO (Extension for Community Healthcare Outcomes) at the University of New Mexico Health Sciences Center (UNMHSC) is to demonopolize knowledge and amplify the capacity to provide best practice care for underserved people all over the world." Additional suggestions for expanded communication can be found below but should also include educational opportunities provided through relevant professional societies for pediatric care providers and opportunities for engagement with disease associated patient advocacy groups.

Education in advance of the development of therapies and examples of the successful use of therapies e.g. SMA will be critical to overcome fear and other public perceptions. Right setting expectations in regards to whether therapies will only apply to those persons newly diagnosed or those at any stage or progression of the disease will be critical as well.

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

Consider the following:

- *Consider how can we address potential disparities in access to these therapies*
- *Consider what can be done to encourage collaboration and increased communication among various stakeholders.*
- *Consider what currently facilitates provision of, or inversely limits access to targeted therapies for patients with rare diseases and list and/or describe*
- *Consider what type of innovations are needed to enable and support development of gene-targeted therapies in a timely fashion*

Addressing disparities in access to new genetic targeted therapies will require us to look beyond the usual players. We must engage community health systems, primary care providers, emergency services and urgent care facilities – to reach people who don't access preventative services but could be followed up after urgent care with this education, awareness and access to interventions.

Clinical trials for new therapies must be planned with inclusion as a principal goal from the start. People of color are more likely to participate in trials if asked by a trusted provider and/or people who look like them. The concerted efforts of the All of Us program to engage all populations is a model for how to intentionally build inclusion into the process.

Incorporating story telling will be key to recruit diverse communities. Elevating the stories across traditional media as well targeted communication channels of people who have gone through gene-targeted therapies, newborn screening, and genetic testing for diagnosis is most likely to be effective. The example of sickle cell anemia outreach and how African Americans immediately understand this example about why genetic testing is relevant to their life and/or their child's health is a good model to replicate.

Using culturally and linguistically appropriate materials (National Class Standards); Federal dollars mean that organizations MUST provide services appropriate to individuals' communication needs (translation into a person's primary language) can be used to hold those organizations accountable for providing those services.

Working with organizations that provide social services could be another way to reach folks after fulfilling primary needs of shelter, food, etc. Having those orgs provide education around health is very important (examples of county health depts/libraries/public transportation that allow one to sign up for multiple social services at one location. Advertisements are effective when placed in waiting rooms, bathrooms, public transport shelters, etc.

Knowing when the screening should occur (like ages 0-3) can help dictate who to partner with in the community and for that target population (Healthy Starts, visiting nurses, WIC programs)

4. ***In general, consider what needs to be improved to deliver gene-targeted therapies to individuals who need them in an efficient, effective, equitable, and timely manner***

Efforts to expedite the diagnosis of epilepsy and the development and dissemination of new gene therapy interventions will have life-changing impacts on people with epilepsy and their families. In parallel, public education campaigns should be launched to help people understand these new therapies and their benefit. Patients and caregivers play an important role in helping enable gene therapies to proceed through advocacy, policy and even legislation as necessary. When treatments ultimately become available – we need to ensure we have an educated and activated population ripe to receive these therapies and their benefits, and to ensure that they are equitably available.

We look forward to working with NCATS team to advance these important goals. Thank you for the opportunity to provide input. For any questions, please contact me on behalf of the undersigned group of organizations at bfureman@efa.org or at 240-476-7127.

Sincerely,

Brandy E. Fureman, Ph.D.
Chief Outcomes Officer
Epilepsy Foundation
On behalf of:

Alliance for the Genetic Etiologies of Neurodevelopmental Disorders and Autism
BPAN Warriors
Bridge the Gap - SYNGAP Education and Research Foundation
CACNA1A Foundation

CFC International
CHAMP1 Research Foundation
Coalition to Cure CHD2, Inc.
COMBINEDBrain
CURE Epilepsy
CureSHANK
Dravet Syndrome Foundation
Dup15q Alliance
Epilepsy Foundation
FamileSCN2A Foundation
Genetic Epilepsy Team Australia
Glut1 Deficiency Foundation
Gould Syndrome Foundation
GRIN2B Foundation
Hope for ULD
International Foundation for CDKL5 Research
International SCN8A Research Alliance
Dravet Syndrome Foundation Spain
KCNQ2 Cure Alliance
Lennox-Gastaut Syndrome (LGS) Foundation
Lightning and Love Foundation
Nonsense mutations foundation
PACS1 Syndrome Research Foundation
Phelan-McDermid Syndrome Foundation
Project 8p Foundation
Rare Epilepsy Network
Ring14 USA
Ring20 Research and Support UK CIO
SLC6A1 Connect
SNAP25 Foundation
STXBP1 Foundation
SynGAP Research Fund
Tbc1d24 Foundation
TESS Research Foundation for SLC13A5 Epilepsy
The Rare Fund
The Schinzel-Giedion Syndrome Foundation
TSC Alliance

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