



June 30, 2021

**Re: Notice Number: NOT-TR-21-027: Request for Information (RFI): Facilitating the Early Diagnosis and Equitable Delivery of Gene-Targeted Therapies to Individuals with Rare Diseases.**

To Whom It May Concern,

The National Organization for Rare Disorders (NORD) appreciates the opportunity to submit comments on the request for information (RFI) captioned above. NORD is a unique federation of voluntary health organizations dedicated to helping the 25-30 million Americans living with a rare disease. We believe that all patients should have access to quality, accessible and affordable health coverage that is best suited to their medical needs.

We thank the National Center for Advancing Translational Sciences (NCATS) for its efforts to facilitate the early identification and the timely, equitable delivery of gene-targeted therapies. Prior to the implementation of the Orphan Drug Act (ODA) in 1983, there were only 30 FDA-approved treatments for rare diseases. As of 2020, 564 treatments have been approved to treat 838 rare conditions.<sup>1</sup> However, despite this important progress, 90% of rare diseases still do not have an FDA-approved treatment, and much remains to be done to bring new cures and treatments to the thousands of rare conditions that currently have no therapeutic option.

Gene-targeted therapies hold incredible promise for patients with rare disorders, as it is estimated that approximately 72% of rare diseases are genetic in origin.<sup>2</sup> Additionally, children under the age of five are disproportionately affected by rare genetic disorders.<sup>3</sup> With many rare disease patients already benefiting from gene-targeted therapies and many new transformative therapies on the horizon, NORD is eager to proactively identify ways to ensure the efficient, effective, and equitable distribution of care for those in the rare disease community that can benefit from gene-targeted therapies.

The following comments provide responses to the considerations set forth by NCATS in the above-titled RFI:

**Question 1:**

*Identification of Individuals that Could Benefit from Gene-Targeted Therapies*

Identifying candidates for gene-targeted therapies is an area that needs careful and robust consideration by all stakeholders. Currently, the United States does very little proactive testing; patients usually present to a health care professional once they have developed one, or several, symptoms. There are several pre-symptomatic screening methods, but our system provides very little incentive to mitigate against future health outcomes. Nevertheless, there are instances where good health practices have been systemically

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<sup>1</sup> IQVIA, NORD (2021). Orphan Drugs in the United States: Rare Disease Innovation and Cost Trends Through 2019. Accessed 6/23/21. <https://rarediseases.org/wp-content/uploads/2021/03/orphan-drugs-in-the-united-states-NRD-2020.pdf>

<sup>2</sup> European Journal Human Genetics (2020). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database.

<sup>3</sup> Journal of Medical Genetics (2019). Case for genome sequencing in infants and children with rare, undiagnosed or genetic diseases.

encouraged and adopted by the U.S., such as regular recommended screenings for cancers like a mammogram or colonoscopy.

One of the programs that excels at equitable, proactive testing is newborn screening. Newborn screening is a key nationwide public health program that tests infants for serious diseases at or around the time of birth. These programs would be a logical fit for a universal genetic testing program because the program effectively reaches nearly every infant born in the U.S. However, there are some serious issues with expanding newborn screening programs outside of their current scope, which is limited to testing for certain conditions for which there is an effective treatment and evidence that early diagnosis and treatment results in better outcomes.

While every state has a newborn screening program, and over 98% of children in the U.S. are screened for certain diseases every year,<sup>4</sup> the programs are not all uniform. There is a wide range in the number of conditions tested for by each state program. In the near term, strengthening newborn screening programs across the country so that they have the resources needed to test for each condition on the Recommended Uniform Screening Panel (RUSP) and add new conditions as tests and treatments are developed must be a high priority.

The current newborn screening program has gaps, such as the inconsistency of screening for all the conditions on the RUSP, that could exacerbate existing disparities in health equity across the country. It also lacks a strong centralized system that could organize the efforts of all the states and territories and help them develop. It is critically important to note that newborn screening is not genetic sequencing. Newborn screening is intended to detect certain diseases that have an effective treatment, not to identify indicators of all genetic diseases. Newborn screening also has well-developed principles that discourage testing for diseases for which there is no treatment as there is a risk of serious harm to the patient with a misdiagnosis.

While it is currently not feasible to sequence every genome at birth in a newborn screening program, as soon as symptoms present themselves and a health care provider has indicators that the disease may be genetic in origin, genetic testing should be considered quickly and made easily available in order to reduce the time to diagnosis. There may also be certain settings where offering or conducting genome sequencing on a regular basis might be effective, particularly Neonatal Intensive Care Units (NICU), and other instances where time to diagnosis and treatment are particularly critical. The strategy of early and often utilization of whole genome sequencing (WGS) in a NICU has actually proven to not only produce better outcomes, but to result in cost savings as well. This point was made by Dr. Kingsmore on day two of the NCATS meeting on Gene-Targeted Therapies: Early Diagnosis and Equitable Delivery (NCATS Meeting).<sup>5</sup>

Americans who have had a family history of genetic disease may seek genetic counseling proactively. However, the vast majority of Americans are likely unaware of the importance of genetic health and may also be more easily dissuaded from taking their genetic health seriously, especially if there are barriers to accessing genetic testing, such as high costs or perceived misuse of the genetic information. In order to identify candidates for gene-targeted therapies, there needs to be a fundamental paradigm shift, which begins with increased education in how patients understand their genetic health. Emphasizing to

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<sup>4</sup> Kennedy Institute of Ethics Journal (2010). Mandatory Versus Voluntary Consent for Newborn Screening? Accessed 6/25/21. <https://muse.jhu.edu/article/413516/summary>

<sup>5</sup> NCATS (2021). Gene-Targeted Therapies: Early Diagnosis and Equitable Delivery (Day 2). Accessed 6/24/21. <https://videocast.nih.gov/watch=41969>

Americans the impact of genetic diseases and providing a way to be proactive about their genetic health will be a key aspect of communicating the benefits of genetic testing.

While genetic testing is essential for identifying genetic diseases, there are some uncertainties and factors that need consideration as we further apply genome sequencing and tests for specific genetic diseases. There are still serious knowledge gaps around variants of unknown significance, or the correlation between a gene variant's existence and its harmful expression in a human. There are also important equity questions around understanding genes of unknown significance in various ethnicities,<sup>6</sup> and efforts to ensure that DNA samples for research that lead to these important discoveries are representative of the population is critical. It is essential to study further and understand if a potentially harmful gene variant will even express itself before undertaking a gene-targeted therapy.

Understanding scientific advancements in the human genome may require developing a centralized system that can act as a knowledge base for geneticists and clinicians so that lessons learned from one setting can be applied in another. Improving the diagnostic process from end to end will be a scientific, regulatory, and societal shift that is fundamental to identifying candidates for gene-targeted therapies.

To date, there are fewer than ten gene-targeted therapies that have been approved by the FDA.<sup>7</sup> However, the American Society of Cell and Gene Therapies estimates that there are hundreds of gene-targeted therapies in development in the U.S.<sup>8</sup> The rapid growth in both scientific knowledge and the pipeline for gene-targeted therapies means that many patients may soon benefit from these treatments. In the near term, the individuals most likely to benefit from gene-targeted therapies are those with genetic diseases that already have dedicated research streams and high levels of public interest, such as many cancers.

However, the long-term goal of researchers and industry should be to identify and treat *all* individuals with genetic disorders. NORD encourages NCATS to pursue a robust translational effort to apply the scientific lessons from gene-targeted therapies broadly to develop more options for patients. The entire ecosystem needs to ensure that lessons from research make the leap into treatments for patients; in too many cases, the scientific knowledge exists, but commercial interest has been difficult to harness into a treatment. However, there has been profound progress in developing gene-targeted therapies in the past several years, and NORD hopes that growth continues. Collective experience from stakeholders and continued scientific research will ideally bring new gene-targeted therapies to more and more patients in an affordable and accessible way.

### *Identification of Rare Diseases that Could Benefit from Gene-Targeted Therapies*

As there are between 5,000-8,000 monogenetic diseases,<sup>9</sup> the likelihood that each condition will have its own dedicated clinical program is very low. It would benefit patients to start in specific disease areas and apply those lessons learned as broadly as possible, which is currently being done in several programs. Technologies such as antisense oligonucleotides (ASO) or adeno-associated virus (AAV) offer the potential to address broad swaths of genetic diseases and maximize the therapeutic potential of gene-

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<sup>6</sup> KHN. Gene Screenings Hold Disease Clues, but Unexplained Anomalies Often Raise Fears. Accessed 6/25/21.

<https://khn.org/news/article/gene-screenings-hold-disease-clues-but-unexplained-anomalies-often-raise-fears/>

<sup>7</sup> FDA. Approved Cellular and Gene Therapy Products. Accessed 5/26/21. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>

<sup>8</sup> ASGCT. Gene, Cell, & RNA Therapy Landscape: Q1 2021. Accessed 6/24/21. [Cell, Gene, & RNA Therapy Landscape \(asgct.org\)](https://www.asgct.org/cell-gene-rna-therapy-landscape)

<sup>9</sup> EUCERD. Report on the State of the Art of Rare Disease Activities in Europe Part II: Key Developments in the Field of Rare Diseases in Europe in 2013. Accessed 6/25/21.

targeted therapies. With ASO and AAV technologies, researchers may develop a platform wherein the vehicle for a therapy remains the same while one or a few parts of that therapeutic agent are switched out to target another disease, a process also known as “plug and play.”

While the mechanism of action is understood, the effectiveness of ASO’s and AAV’s (or other viral vectors) depends on adequate delivery (“targeting”) to the tissues in which important pathology occurs and satisfactory delivery methods for all potentially relevant tissues are not yet available or proven. Currently, some diseases cannot be well targeted due to limits on the technologies we have available. For instance, an AAV vector may not be large enough to contain the entire therapeutic gene, or an AAV serotype or an ASO may not be effectively taken up by the target tissue. Thus, research to expand the list of tissues, rather than individual diseases, that can be successfully targeted should remain a priority. In the future, with more extensive tools for targeting different tissues, the list of diseases that are effectively amenable to treatment will be expanded, potentially to all genetic diseases diagnosed before irreparable tissue damage has occurred.

In the near term, to proactively identify those patients who could benefit from gene-targeted therapeutics, consideration must be given to how to best educate individuals in the U.S. to advocate for genetic testing, including especially whole exome or whole genome DNA sequencing when it is appropriate. Furthermore, steps must be taken to ensure appropriate health insurance coverage and reimbursement for such services, so that these powerful and efficient testing methods are ultimately incorporated into routine care. The health care system has found ways to incentivize regular check-ups and empowered people to take care of their health; incorporating genetic health into that process is equally as critical.

#### *Timing of Identifying Patients with Genetic Disorders and Ending the Diagnostic Odyssey*

Early identification and diagnosis of patients is especially critical for many genetic diseases. Many genetic diseases are degenerative, meaning that once a patient’s function has been lost, it cannot be restored. Typically, the earlier a genetic disease is identified and treated, the better the outcomes for the patient; therefore, the ideal time to test for an inherited genetic disease is in utero or at birth. Newborn screening, as mentioned above, is a prime example of as close to an ideal time to diagnose and treat as is possible. In most cases identified by newborn screening, the infant is pre-symptomatic, and early intervention can treat or save the child’s life, dramatically reducing the effects of the disease over the entire life of the patient. This has incredible positive downstream impacts on the child, their family, and the healthcare system.

There may also be other times during an individual’s life where it makes sense to do genetic sequencing. As science develops, it might be recommended to have sequencing done at certain milestones (as discussed on multiple occasions during the NCATS Meeting) to promote robust genetic health. There also may be certain life events that incline someone to undergo genetic testing. For instance, people thinking about conceiving a child might be encouraged to take a genetic screen by a primary care physician or obstetrician-gynecologist to identify potential heritable conditions they could pass to their children.

As a matter of timing, *if a child or adult starts presenting symptoms of a disease, and their health care provider believes there could be a genetic origin, then they should consider broad genetic testing early in the diagnostic process.* Time is extremely important in these situations, and efforts to encourage and enable physicians to order appropriate genetic testing can have a tremendous impact. Genetic testing must

be accessible, affordable, and available to all Americans so they can take control of their genetic health, enabling earlier identification and more effective treatment of genetic diseases.

Gene-targeted therapies are likely most appropriate for severe diseases and/or diseases with no other effective therapy. While it may not be cost-effective currently to test the entire population, because the benefit of therapy is often greatest when applied early, and because using traditional diagnostic approaches of sequential clinical evaluations and disease-specific tests often leads to very long “diagnostic odysseys” and delayed diagnosis, for the fraction of patients presenting with features that suggest a possible underlying genetic cause, broad genetic testing (such as whole-exome sequencing or whole genome sequencing) should be made rapidly available. As genetic sequencing becomes more cost-effective, once there is reason to believe a patient may have a serious genetic disease, appropriate genetic testing needs to be made available to a patient per the advice of a geneticist, or other qualified healthcare provider. In particular, ending or greatly ameliorating the diagnostic odyssey for many patients via WGS is an achievable near-term step that will have a huge impact on patients. WGS was previously inaccessible until relatively recently because of lack of knowledge and cost, both issues have become vastly more manageable recently, and all signs indicate that the trend of increased understanding and lower costs will make WGS more accessible in the future.

## **Question 2:**

### *Infrastructure: Current Mechanisms and Improvements for Diagnosing and Identifying Individuals with Rare Diseases for Gene-Targeted Therapies*

Currently, when diagnosing a condition, the diagnostic process for physicians is very similar regardless of the disease. Typically, patients will present with symptoms, and physicians will often use a stepwise approach to attempt to determine the cause of those symptoms, in many cases spotting patterns or clues to guide their professional opinion. In cases of rare diseases, regardless of origin, this process is much more challenging because many rare diseases will have never been seen before by the individual physician, and signs and symptoms of any one genetic disorder may overlap with those of other diseases, which can further complicate the diagnostic process. The diagnostic odyssey, as mentioned above, is the result of this process of trying to match a pattern of symptoms to a rare or even yet-to-be-discovered disease. By encouraging genetic testing earlier in the process, we can very often shorten the time to diagnosis.

After a determination is made by a physician that a disease may be genetic in origin, there are often several options for testing that vary primarily by the breadth of the testing. The choice of the most appropriate testing strategy usually depends on the degrees of confidence the physician has that he or she can predict the specific gene or class of genes most likely responsible for the individual patient’s clinical presentation. If a physician is confident that they know which gene is causing the disease, they may order testing for mutations (i.e., pathogenic DNA variants) in just one specific gene. Alternatively, if they believe they know which category of diseases the patient’s case represents but they can’t readily identify the specific disease or gene involved, then the physician may order a panel test that includes many genes that can produce diseases in a certain category that have overlapping constellations of signs and symptoms. For a panel test, the cost is somewhat lower than genome-wide genetic testing, and the risk of getting a false signal is also lower than for whole-genome sequencing. Usually, if a physician is not confident which specific category of genes includes the cause of an individual patient’s disease, but they

are confident that their disease is likely genetic in origin, then whole exome or genome sequencing might be the best option.

In the event that the results from the genetic sequencing are unclear, there are further options, such as sequencing at the RNA level, or other forms of RNA expression testing, which in some cases reveals what the whole genome or exome sequencing didn't identify and can help provide clues about the nature and location of the causative DNA variant and thus where to focus analysis of the patient's DNA sequence. These broad DNA and special RNA testing procedures are very powerful diagnostic tools when used and interpreted properly. However, there are often practical issues for patients in getting these newer testing procedures covered by an insurer; therefore, in addition to steps to further reduce the costs of performing such testing, which is declining over time, the government and/or insurance providers should take steps to ensure that when ordered by a qualified healthcare provider these tests can be affordably accessed by any patient.

Another factor to consider when examining real-world physician practices is that the known availability of a therapy can be the primary motivator for ordering the tests. Physicians will often order tests for those diseases they know may have a treatment, meaning that patients with diseases without a specific treatment known to that physician may not be diagnosed properly. Similarly, in cases where a diagnosis is possible, but it is not currently known that this would impact the treatment plan for the patient, physicians are unlikely to order thorough diagnostic tests because it puts additional burdens on the patients to pay for these tests. Tragically, some patients who have not received appropriate and sufficiently broad genetic testing are given an inaccurate clinical diagnosis and an opportunity to effectively treat their real diagnosis is missed. In order to change this paradigm of genetic testing reluctance, physicians must be encouraged to thoroughly test to ensure there are no mistakes in the diagnosis and that opportunities for more effective treatment are not missed.

NORD believes that the more the patients are armed with their own, correct diagnosis the more power they have as a collective. Patients with an accurate diagnosis can form communities to support each other and advocate on their behalf with more authority, including advocating for treatments for their disease.

### *Public-Private Partnerships to Support Access to Gene- Targeted Therapies*

The field of gene-targeted therapy is developing and evolving every day, and to date, the key to that growth has often been public-private partnerships (PPP) that exist for genetic diseases. Right now, these programs (and others) are doing yeoman's work to pave a path forward scientifically.

In the future, several established PPPs at FDA and NCATS will continue to make progress in moving the needle for patients, including the Gene Therapy Platform for Rare Diseases in the Therapeutics for Rare and Neglected Diseases (TRND).<sup>10</sup>

At the FDA, the Rare Diseases Cure Accelerator (RDCA) program offers tremendous potential to lay the groundwork for the development of gene-targeted therapies for a wide range of therapeutic options for

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<sup>10</sup> NIH. National Center for Advancing Translational Science. Gene Therapy Platform for Rare Diseases. Accessed 5/23/21. <https://ncats.nih.gov/trnd/projects/gene-therapy>

rare disease patients.<sup>11</sup> Obviously, critical to access to gene-targeted therapies is approval by the FDA. To do that will require natural history studies, patient-centered outcomes, and clinical trials, which can get extremely complicated in the area of gene-targeted therapies for rare diseases. Efforts like the RDCA which attempt to bridge some of those concerns will lay the groundwork for future innovative drug development methods that focus on the patients.

Another important initiative at Foundation for the National Institutes for Health is the “Bespoke Gene Therapy Consortium” aimed at bringing therapies to patients for extremely rare conditions that may not otherwise be pursued due to the very limited or absent potential for commercial profit in such cases.<sup>12</sup> The lessons learned from these programs have enormous potential for broader genetic diseases.

### *System Solvency*

The cost of whole-genome and exome sequencing has been decreasing in the past few years, and it is important for that trend to continue as we further invest in the science and technology of diagnosing and treating genetic diseases. There also needs to be continued investment into understanding genetic diseases, particularly their pathologies. Understanding symptoms and progression as characterized in a natural history study will hopefully lead patients to diagnosis and treatments faster.

In order to maintain sustainability for gene-targeted therapies, especially ones for diseases with small patient populations, we need to reduce inefficiencies and streamline as many processes in the development process as we can, particularly dosing and toxicology studies, to lower costs so that these products can scale and be accessible to patients. Ideally, as we gain more experience with gene-targeted therapies, stakeholders will find ways to reduce inefficiencies and cut manufacturing and development costs.

### *Communicating Information on Gene-Targeted Therapies to Primary Care Physicians and other Healthcare Providers*

In order to educate more physicians about gene-targeted therapies, there must be a well-established effort to bring this knowledge to providers in every community across the country. In educational settings, teaching both primary care providers and specialists about the importance of encouraging early, or even pre-symptomatic, genetic testing for patients is an important first step. But, while it may be easier to incorporate gene-targeted education into medical schools, the field is developing so rapidly that there must be ongoing education of established providers both in and outside of medical schools and academia. Currently, a physician is only likely to learn about options for a gene-targeted therapy within the context of an approved and marketed treatment for a specific disorder. Thus, there is much more that could be done, especially more education for providers on gene-targeted therapies generally. Educating physicians on gene-targeted therapies should also be accompanied by also incorporating information regarding the ever-increasing utility of seeking an accurate and specific diagnosis through genetic testing. Both a short- and long-term solution to this issue might be found in creating a centralized educational resource body, either within the federal government, academia, or via a public-private partnership that can be updated and curated as scientific knowledge advances, as was suggested during the NCATS Meeting. The process

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<sup>11</sup> FDA. Rare Disease Cures Accelerator. Accessed 5/23/21. <https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator>

<sup>12</sup> FNIH. Bespoke Gene Therapy Consortium. Accessed 5/23/21. <https://fnih.org/BGTC>

of gathering and utilizing this information must also be accessible and participated in by a wide range of stakeholders, ensuring diverse communities are able to access and contribute to this knowledge base to better enable equitable development and access to gene-targeted therapies.

### *Communication with Healthcare Providers, Patients, and Families Regarding Gene-Targeted Therapies*

Methods of communicating to patients, caregivers, and physicians about both genetic diseases and gene-targeted therapies are important to consider. Currently, many physicians feel uncomfortable discussing gene-targeted therapies with their patients and would rather refer them to another physician.<sup>13</sup> Educational resources need to be more widely available on both early diagnosis (through increased testing) and the nature of gene-targeted therapies. Communications should address things like concerns from patients about what gene-targeted therapy is and how they are different from traditional drugs.

All communication to patients, irrespective of the information included, needs to be culturally competent and understandable to a layperson. Written communication should be offered in multiple formats (print or online) for digestion by any age group. There also needs to be consideration of tone and a process for discussing sensitive issues. Gene-targeted therapies have the potential to revolutionize personalized care, but many Americans think that the science and drug development is more advanced than it currently is; so, managing expectations regarding gene-targeted therapies will also be important.

NORD encourages NCATS to explore including patient groups in their efforts. Patient organizations are often already established and trusted within the patient community and often develop and distribute resources to help patients understand their diseases or therapeutic options. In order to have effective communication about gene-targeted therapies, all stakeholders should keep their audience in mind, use clear and easy to understand language, and offer as many different types of communication as possible (one-pagers, videos, pamphlets, websites, different languages, accessible to the visually or hearing impaired, etc.). Many patients often don't know where to turn next after a diagnosis. As mentioned during the NCATS Meeting, a toolkit or guide for clinicians and patients to navigate the post-diagnosis period is a resource that will have a near term immediate impact on patients if promulgated efficiently. Many times, just after a diagnosis, there are feelings of isolation, and many patients are overwhelmed at the task ahead. NORD and other patient groups work to provide patients with the resources and community they need to navigate this difficult time, but there is always more that can be done to reach patients and guide them during this time.

### **Question 3:**

#### *Ensuring Equitable Access to Approved Gene-Targeted Therapies*

The federal government can take a number of actions to address disparities in access to innovative gene-targeted therapies and to facilitate the increased provision of life-saving cures to patients with rare disorders. Gene-targeted therapies are among the most expensive treatments on the market, though they may result in long-term overall savings due to their curative potential. As a response to high up-front costs, payors are increasingly placing utilization management barriers between patients and gene-targeted therapies. In addition, some state Medicaid programs have sought the authority to restrict their

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<sup>13</sup> Neurology Reviews (2020). Gene Therapy Survey Highlights: Knowledge Gaps and Educational Opportunities. Accessed 6/25/21. [https://www.neurologyreviews-digital.com/neurologyreviews/nord\\_march\\_2020/MobilePagedReplica.action?pm=2&folio=94#pg104](https://www.neurologyreviews-digital.com/neurologyreviews/nord_march_2020/MobilePagedReplica.action?pm=2&folio=94#pg104)

formularies or otherwise delay patient access to drugs approved through the FDA pathways traditionally utilized by these treatments.

Another obstacle to timely diagnosis and treatment of rare genetic disorders is a lack of health care providers with expertise in a specific rare disease, including the size and availability of the genetics workforce. Many people with rare diseases face geographic barriers to accessing treatment. In the case of many rare diseases, there are only a handful of specialists nationwide, or even worldwide, who have expertise in a given rare condition. As a result, patients often travel long distances to access their treating providers, or to access facilities that are equipped to administer a gene-targeted therapy. According to a survey conducted by NORD in 2019, 39% of rare disease patients needed to travel 60 or more miles in order to see a provider.<sup>14</sup> In addition, many states do not have a sufficient number of trained geneticists or other appropriate providers, a problem that can delay diagnosis and treatment for genetic conditions. This can exacerbate insurance and affordability-related challenges for patients who must travel long distances and potentially out-of-network to access care.

We will discuss each of these issues in further depth below.

### *Access and Affordability for Patients*

As the pace of innovation in the biopharmaceutical industry quickens, the prices for these innovations are increasing significantly and, in some cases, are beyond the reach of patients. Gene-targeted therapies can result in a lifetime of benefit but be exceptionally costly for a single dose. Though this may result in net savings to the overall health care system in the long run, it is incredibly difficult for patients and payors to absorb the initial price and may drive payors to either not cover gene-targeted therapies entirely or use utilization management techniques to delay or discourage their use.

According to a 2019 survey of rare disease patients and caregivers conducted by NORD, 61% of patients had been denied or faced delays accessing treatments that required pre-approval from an insurance company.<sup>15</sup> NORD has already observed instances where payors have placed utilization management barriers between patients and gene-targeted therapies in order to discourage their uptake. For example, in June of 2020, North Carolina's Division of Medical Assistance released the proposed "Outpatient Pharmacy Prior Approval Criteria for Zolgensma" (Proposed Prior Approval Criteria).<sup>16</sup> The Proposed Prior Approval Criteria required that a child covered by the state's Medicaid program present symptoms of spinal muscular atrophy (SMA) as a condition for coverage for the gene-targeted therapy Zolgensma. This would mean that a newborn with SMA, who had been identified through the state's newborn screening program, would be denied treatment until irreversible nerve damage had already occurred, resulting in symptoms. This requirement is not consistent with Zolgensma's FDA-approved label, which does not require that a child presents symptoms prior to treatment<sup>17</sup> and runs

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<sup>14</sup> National Organization for Rare Disorders (2020). Barriers and Facilitators to Rare Disease Diagnosis, Care and Treatment: 30-year Follow-up. Accessed 6/25/21. [https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report\\_FNL-2.pdf](https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf)

<sup>15</sup> National Organization for Rare Disorders (2020). Barriers and Facilitators to Rare Disease Diagnosis, Care and Treatment: 30-year Follow-up. Accessed 6/25/21. [https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report\\_FNL-2.pdf](https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf)

<sup>16</sup> North Carolina Division of Medical Assistance (2020). Prior Approval Criteria for Zolgensma. Accessed 6/25/21. [https://files.nc.gov/ncdma/documents/GetInvolved/Public\\_Notices/Public-Comment---PA-Criteria-Zolgensma.pdf](https://files.nc.gov/ncdma/documents/GetInvolved/Public_Notices/Public-Comment---PA-Criteria-Zolgensma.pdf)

<sup>17</sup> Zolgensma [package insert]. AveXis, Inc (2019). Accessed 6/25/21. <https://www.fda.gov/vaccines-blood-biologics/zolgensma>

counter to the “preventative thrust” of federal Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standards.<sup>18</sup>

NORD is also concerned that states may place arbitrary and harmful barriers between patients and gene-targeted therapies that receive approval through one of the FDA’s expedited pathways (i.e., accelerated approval, fast-track, or a breakthrough designation). In 2019 the National Governors Association (NGA) stated that Medicaid programs should be able to “exclude from their formularies or receive enhanced federal matching funds for select fast-tracked, first-in-class drugs.”<sup>19</sup> Two states, Massachusetts<sup>20</sup> and Tennessee,<sup>21</sup> have sought federal waivers from Medicaid’s broad coverage requirements, and other states have explored implementing delays or other targeted utilization management barriers for expedited drugs.<sup>22</sup> These examples from state Medicaid programs are especially concerning in the context of equitable access to gene-targeted therapies. Medicaid provides insurance coverage to millions of low-income Americans, many of whom have substantial health care needs, and is an especially significant source of coverage for Black and Hispanic Americans.<sup>23</sup> Finally, Medicaid is the largest payor in the nation for children with special health care needs, a population that is particularly impacted by new gene-targeted therapies.<sup>24</sup>

In the commercial insurance market, it is important that the costs of gene-targeted therapies are not shifted disproportionately onto patients, as that would inevitably place access to therapies outside of the reach of many families. Utilization management tools are also used by payors in the commercial market and can be extremely time-consuming for both patients and providers to navigate. This can delay necessary treatment, allowing disease progression and resulting in additional health care costs while approvals are being sought. This increases the out-of-pocket burden for the patient. In addition, some insurance plans use coinsurance, in which patients are responsible for a percentage of the diagnostics or medications cost, rather than a flat copayment. In the case of gene-targeted therapies, particularly for those with high-deductible health plans, this could translate to significant out-of-pocket costs for the associated diagnostics and the treatment, not including any other necessary care such as blood work and post-treatment monitoring and rendering the gene-targeted therapy unaffordable.

The development of new gene-targeted therapies is meaningless to patients if they cannot access them, and it is essential that patients are not denied potentially life-saving new gene-targeted therapies in the name of cost-savings. Gene-targeted therapies are fundamentally different from most previously developed treatments for individual diseases, and as greater numbers of one-time use therapies gain FDA

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<sup>18</sup> Centers for Medicare and Medicaid Services. (2014). *EPSDT - A Guide for States: Coverage in the Medicaid Benefit for Children and Adolescents*. Accessed 6/25/21. [https://www.medicaid.gov/sites/default/files/2019-12/epsdt\\_coverage\\_guide.pdf](https://www.medicaid.gov/sites/default/files/2019-12/epsdt_coverage_guide.pdf)

<sup>19</sup> 2019 principles for federal action to address health care costs. National Governors Association. Accessed 6/25/21. [https://www.nga.org/wp-content/uploads/dlm\\_uploads/2019/05/NGA-Health-Care-Costs-Principles-FINAL.pdf](https://www.nga.org/wp-content/uploads/dlm_uploads/2019/05/NGA-Health-Care-Costs-Principles-FINAL.pdf)

<sup>20</sup> MassHealth Section 1115 demonstration amendment request (2017). Medicaid.gov. Accessed 6/25/21. <https://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Waivers/1115/downloads/ma/ma-masshealth-pa3.pdf>

<sup>21</sup> TennCare II Demonstration: amendment 42 modified block grant and accountability (2019). Accessed 6/25/21 <https://www.tn.gov/content/dam/tn/tenncare/documents2/Amendment42FinalVersion.pdf>

<sup>22</sup> Meeting of the Fast Track Drugs & Emerging Technologies Workgroup (2020) Accessed 6/25/21. [https://townhall.virginia.gov/L/GetFile.cfm?File=Meeting%5C64%5C31252%5CMinutes\\_DMAS\\_31252\\_v1.pdf](https://townhall.virginia.gov/L/GetFile.cfm?File=Meeting%5C64%5C31252%5CMinutes_DMAS_31252_v1.pdf)

<sup>23</sup> Kaiser Family Foundation. (2019) Distribution of the Nonelderly with Medicaid by Race/Ethnicity. Accessed 6/25/21. <https://www.kff.org/medicaid/state-indicator/medicaid-distribution-nonelderly-by-raceethnicity/?dataView=0&currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22,%7D>

<sup>24</sup> American Academy of Pediatrics. (2018). Medicaid facts. Accessed 6/25/21. [https://www.aap.org/en-us/Documents/federaladvocacy\\_medicaidfactsheet\\_all\\_states.pdf](https://www.aap.org/en-us/Documents/federaladvocacy_medicaidfactsheet_all_states.pdf)

approval our methods of payment and reimbursement may need to likewise be reimagined. As payers, manufacturers, and policymakers work together to develop new coverage and reimbursement models, NORD urges them to keep patient access and affordability as a chief priority while enabling a sustainable health care system overall.

### *Limits to the Genetics Workforce*

In addition to the cost and affordability issues discussed above, patients with rare disorders may find their diagnosis and treatment delayed due to a lack of access to qualified providers. The genetics workforce, primarily consisting of medical geneticists and genetic counselors, plays an important role in the diagnosis and treatment of rare genetic disorders. The workforce has expanded slowly over time, but provider shortages persist. In addition, the general health care workforce receives limited genetics education and is ill-equipped to incorporate genetics into practice, exacerbating access issues due to the limited availability of medical geneticists.<sup>25</sup> For example, in a survey of medical providers (n=1,472) conducted by Frontline Medical Communications (FMC) in collaboration with NORD, respondents reported a “low level of comfort discussing gene therapy with patients.” Indeed, 62% of respondents “reported that they preferred to refer patients to an expert to discuss gene therapy.” Only 20% of respondents indicated that they discuss gene therapy options with their patients.<sup>26</sup>

Access to experts in genetics and gene-targeted therapies also varies widely by region. According to an analysis by the Government Accountability Office (GAO), there are more genetic counselors and medical geneticists per 500,000 people in the northeastern and some midwestern and western states, and lower proportions in other areas of the country. Three states have less than one genetic counselor per 500,000 people, and twelve states have less than one medical geneticist per 500,000 people.<sup>27</sup> Surveys of *practicing* clinical geneticists reveal even more stark geographic barriers, with 14 states reportedly having five or fewer currently certified clinical geneticists and one state with no practicing clinical geneticists.<sup>28</sup> Many states with large rural areas – such as Wyoming, Mississippi, and Oklahoma – have a particularly low concentration of genetic counselors and medical geneticists.<sup>29</sup> In one study of genetic counselors practicing in rural areas, researchers found that patients often must travel far distances to access genetics services, a time and financial commitment that many patients may be unable to shoulder.<sup>30</sup> Additionally, 30% of genetic counselors surveyed reported new patient wait times of longer than one month.<sup>31</sup>

A well-trained workforce is necessary to meet demands for genetic services as advances in gene-targeted therapies continue to be made. NORD encourages the NIH to consider the “human infrastructure” that is

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<sup>25</sup> SACGHS (Secretary’s Advisory Committee on Genetics, Health, and Society) (2011). *Genetics Education and Training: Report of the Secretary’s Advisory Committee on Genetics, Health, and Society*. NIH Office of Science Policy. Accessed 6/25/21. [https://osp.od.nih.gov/wpcontent/uploads/2013/11/SACGHS\\_education\\_report\\_2011.pdf](https://osp.od.nih.gov/wpcontent/uploads/2013/11/SACGHS_education_report_2011.pdf)

<sup>26</sup> Frontline Medical Communications (2020). Gene Therapy Survey Highlights: Knowledge Gaps and Educational opportunities. *Neurology Review*. Accessed 6/25/21. [https://www.neurologyreviews-digital.com/neurologyreviews/nord\\_march\\_2020/MobilePagedReplica.action?pm=2&folio=94#pg104](https://www.neurologyreviews-digital.com/neurologyreviews/nord_march_2020/MobilePagedReplica.action?pm=2&folio=94#pg104)

<sup>27</sup> GAO (2020). *Information on Genetic Counselor and Medical Geneticist Workforces*. Accessed 6/25/21. <https://www.gao.gov/assets/710/708545.pdf>

<sup>28</sup> Jenkins, B.D., Fischer, C.G., Polito, C.A. *et al.* (2020). The 2019 US medical genetics workforce: a focus on clinical genetics. *Genet Med*. Accessed 6/25/21. <https://doi.org/10.1038/s41436-021-01162-5>

<sup>29</sup> GAO (2020). *Information on Genetic Counselor and Medical Geneticist Workforces*. Accessed 6/25/21. <https://www.gao.gov/assets/710/708545.pdf>

<sup>30</sup> Emmet, M., Stein, Q., Thorpe, E. & Campion, M. (2018). Experiences of Genetic Counselors Practicing in Rural Areas. *Journal of Genetic Counseling*, 27, 140–154. doi.org/10.1007/s10897-017-0131-6. Accessed 6/25/21.

<sup>31</sup> *Ibid.*

needed to expand access to these therapies in an equitable manner, particularly in rural or underserved communities.

**Conclusion**

NORD again thanks NCATs for the opportunity to provide comments. We look forward to working with the Center to deliver innovative new treatments and cures to patients with rare disorders. For questions regarding NORD or the above comments, please contact Rachel Sher at [rsher@rarediseases.org](mailto:rsher@rarediseases.org) or 202-588-5700.

Sincerely,



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