

RARE PEDIATRIC DISEASES

SPECIAL REPORT



Pediatric News®



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Get the Diagnostic Work Done Swiftly

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EDITOR'S NOTE



Catherine Cooper
Nellist

Thousands of rare diseases have been identified, but only 35 core conditions are on the federal Recommended Uniform Screening Panel (RUSP). But the majority of states don't screen for all 35 conditions. Read on to learn about the pros and cons of state-by-state differences in newborn screening for rare disorders. But newborn screening is not the only way to learn about a child's rare disease. There is genetic screening, and now it is more widely available than ever. But how to make sense of that information? Certified genetic counselors

will help, but health care providers need education about what to do when a rare disease is diagnosed.

In this *Rare Pediatric Diseases Special Report*, there are resources for you as health care providers and for your patients provided by the National Institutes of Health and by the National Organization for Rare Disorders. Explore a synopsis of existing and emerging treatments of three rare epileptic encephalopathies that occur in infancy and early childhood—West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome. Learn about important advancements in the treatment of three rare pediatric neuromuscular disorders—spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), and X-linked myotubular myopathy (XLMTM)—and how improved quality of life and survival will challenge current systems of transition care. Read about the progress made in cell and gene therapies for neurological diseases. Learn about early research on treatments for Angelman syndrome and X-linked chronic granulomatous disease. I hope you enjoy reading this special report.

—Catherine Cooper Nellist, Editor, *Pediatric News*

A NOTE FROM NORD



Sika Dunyoh

Welcome to our first issue of the *Rare Pediatric Disease Special Report*. The National Organization for Rare Disorders® (NORD) is proud to collaborate with *Pediatric News* and medical experts to bring you information on timely and important topics related to caring for children affected by rare medical conditions. We value this opportunity to speak directly to the healthcare professionals who play such a critically important role in the lives of the patients and families whom we represent.

Topics covered in this issue—such as newborn screening, cell and gene therapies and advances in addressing diagnostic challenges—reflect that we are in a time of incredible transformation in the rare disease space with rapidly expanding knowledge and research opportunities. More than half of the new medical treatments approved by the US Food and Drug Administration in 2018 were for rare diseases, and many of these new products represent significant advances over previously available treatment options. This includes, for instance, products that employ precision medicine to help identify the patients most likely to benefit from specific therapies.

With more than 7,000 medical conditions now recognized as rare diseases by the National Institutes of Health—and new ones being identified on a regular basis—it is increasingly difficult for the busy clinician to stay abreast of the latest thinking and advances related to these conditions. Furthermore, over half of those affected by rare diseases are children. Professionals providing pediatric care have a particular need for up-to-date information related to rare disease diagnosis and treatment.

This is why NORD is so grateful for this opportunity to present information about the status of rare disease management, innovative tools for diagnosis and new treatment options for children affected by rare diseases. We invite you to visit the NORD website often (rarediseases.org) for updates, disease state information, as well as research funding opportunities. We also encourage you to watch for other educational resources provided by NORD for medical professionals, including free webinars, CME resources and our annual NORD Rare Diseases and Orphan Products Breakthrough Summit, which takes place in Washington, DC each year in October.

—Sika Dunyoh, Director of Education Programs,
National Organization for Rare Disorders (NORD)

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Rare Diseases Pose a Pressing Challenge: Get the Diagnostic Work Done Swiftly



Nicholas Munafo and
Ronald DeBellis, PharmD

Roughly 8,700 rare diseases have been identified as we write. Yet, coming to a diagnosis for these rare and ultrarare diseases continues to be a challenge in what is considered to be the rare disease space. With the average time to diagnosis for rare diseases ranging from 7 to 9 years, it remains difficult for patients, families, and providers to arrive at a timely diagnosis. The rare disease community, an already a small segment of the greater medical community, is searching desperately for answers.

The Digital Age Is Upon Us. Is That Good?

Advancements in technology are moving faster than policy and education initiatives are able to keep pace. We live in a time when at-home genetic tests are not only a possibility, they are a reality. We are at the forefront of gene therapy and gene technology, where the potential for cures of many rare diseases seems ever so close.

But these advancements in technology have outpaced our ability to recognize patients who require these complex treatments. Thousands of diseases, rare and common, are paired with a limited medical workforce, symptom overlap, and lack of provider awareness. Couple these realities with the limited time to think deeply and intuitively in a fast-paced clinical world, and what seems to be a simple step in care becomes increasingly complicated. The pressing question is how we solve this ever-crippling challenge of decreasing time to diagnosis.

Getting Answers Early and Often

Newborn screening is the practice of testing every newborn for harmful or potentially fatal disorders otherwise not apparent at birth—a relatively simple and noninvasive test. The physician collects blood at birth or shortly after, and a panel of

tests is run by the laboratory looking for a limited number of predefined conditions. These conditions—cystic fibrosis, phenylketonuria, and sickle cell disease (to name a few)—are often rare but, if detected early, can accelerate treatment, thus potentially increasing quality of life and decreasing irreversible anatomic, neurologic, and physical damage.

Why, one might question, if we have the ability to detect these conditions, are we struggling to diagnose rare diseases, on a broader scale? There are no easy answers. The answer to that question is multifactorial, and the solution is more complicated than just making a simple change.

The federal government recognizes and continues to add conditions to the recommended newborn screening panel, but that is all the panel is: recommended. Each state has its own legislature, which determines constituent tests of the screening panel required at birth; panels therefore vary, leading to a discrepancy in the continuity of care at the state level. Without standardization of newborn screening panels, there will always be a discrepancy in which diseases are diagnosed and which go undiagnosed, and therefore which patients will benefit while others do not.

In many respects, newborn screening has the opportunity to diagnose rare disorders in a proactive fashion; without adequate testing, however, we revert to a reactive medical model.

We also run into a predicament: there are more than 8,000 rare diseases. To look for every rare disease individually on a panel is unrealistic and cost ineffective.

Newborn screening panels are only as good as the diseases they look for. For rare diseases that remain undiscovered, screening is, obviously, impossible.

Last, once a patient is given a diagnosis of a rare disorder, finding the appropriate team of medical specialists to put a care plan in place remains difficult.

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Not All Genetic Tests Are Created Equal

As health care moves toward a patient-centered model, patients and families are becoming their own advocates for diagnosis and disease education. The burden should not be on the family to come up with a diagnosis, only to have it confirmed later or accepted by the care team. Patients and families are their best advocates in the current model. Understanding what to do with information and how to use it is key.

This is when genetic testing comes into play. By using the services of companies such as 23andMe, people can send out a specimen and, after a short time, receive validated results on their ancestry and certain aspects of health and wellness (as allowed by the US Food and Drug Administration), include genetic health risks, carrier status, and traits. Not only are these tests validated, but they also meet Food and Drug Administration requirements for specificity. Once this information is gathered, however, what is someone to do with

Patients and families are their best advocates in the current model. Understanding what to do with information and how to use it is key.

the overwhelming genetic information they have just received in an e-mail?

Enter the genetic counselor. A staple in the rare disease space, genetic counselors can take the lead in guiding patients and care teams to a diagnosis. Genetic counselors are health professionals who specialize in genetic testing; their roles can include ordering genetic tests for patients, working with physicians and health-care teams to interpret genetic results, and counseling families on genetic results and their implications.

A recurring problem in the world of health care is access, however. As the frequency and availability of genetic testing increases, demand for genetic counselors is also on the rise. This leads to a long wait—months in some regions—to connect with genetic counselors. Such a lag can delay the time to diagnosis and frustrate families who have test results in hand but cannot have them interpreted or utilize them.

At the 2018 Rare Disease and Orphan Products Breakthrough Summit, Ellen Matloff, founder, president, and chief executive officer of My Gene Counsel, urged people who are seeking a genetic counselor to at the very least look for a certified genetic counselor through the National Society of Genetic

Counselors (<https://www.nsgc.org>).¹ Some enterprises offer telephone counseling instead of an in-person appointment, allowing for direct access to a counselor within 48 to 72 hours in many cases. Telephone counseling might cut down the wait time to reach a genetic counselor face to face by months.

If You Don't Know Where You're Coming From ...

Health care provider education is key to a timely diagnosis. It takes a village. In saying that, the rare disease community needs to work together as advocates to promote continuing education on rare diseases. Knowing when something does not look right and how to interpret symptoms, however general they are, is an important gap in education. It is difficult enough for primary care providers and specialists to come to a diagnosis. One school of thought is to create health care teams that work solely on diagnosis. This approach would do the following:

- concentrate resources on finding the right diagnosis without spreading resources thin in other areas
- include access to genetic testing
- offer provider education on rare-disease diagnosis
- initiate appropriate steps once a diagnosis is achieved
- collaborate with industry to decrease time to diagnosis.

... You Won't Know Where You're Going

It is challenge enough to get a rare disease diagnosed—let alone an ultrarare disease such as spinal muscular atrophy (SMA). At the 2018 Rare Disease and Orphan Products Breakthrough Summit, Jaimie Vickery, vice president of policy and advocacy at Cure SMA, explained that health care, to move in a positive direction, needs the tools and education to distinguish between rare and ultrarare disease, such as SMA, which is difficult to find.¹ For diseases such as SMA, which often affect young children, time to diagnosis is critical. The earlier the disease is caught and treated, the greater the reduction in damage. Treatment of rare genetic diseases can prevent, but cannot repair, damage.

There is movement now in the right direction. Industry is collaborating with the community to increase access to genetic testing and bridge timely diagnosis and treatment. Recently announced by Sanofi Genzyme and PerkinElmer is the launch of their Lantern Project, which will provide genetic testing for patients whose physicians suspect might be suffering from one of more than 40 known lysosomal storage disorders. This is a big step in the right direction toward access to genetic testing and decreasing time to diagnosis.

Yet challenges remain. Tests provided through the Lantern Project are not comprehensive: they are only for patients suspected of having a lysosomal storage disorder. In

addition, participating companies will test only for diseases for which they have, or are developing, a treatment. This leaves a large unmet need in diagnostics for diseases.

Mysterious Diseases Eluding Diagnosis: Programs With Possible Answers

William Gahl, MD, of the National Human Genome Research Institute within the National Institutes of Health (NIH), proposes that databases on genetic exomes and phenotypes can be used to search for signs and symptoms. These databases need to be shared (while maintaining privacy) to compile large amounts of data that can be used to accelerate diagnosis and form a worldwide database that is queried by geneticists and providers who have a patient exhibiting a particular set of symptoms. Such a system can also guide patients to the right diagnostician.

For patients whose symptom presentation is multisystemic, Dr. Gahl urges them, and their families, to take control of their care. It is essential for the family and medical center to organize and orchestrate all aspects of diagnosis.

The NIH also has an Undiagnosed Diseases Network (<https://undiagnosed.hms.harvard.edu>), established in 2008 by Dr. Gahl, to provide answers to patients with a mysterious disease that has eluded diagnosis. This program looks at specific patients for 5 days in an inpatient setting. All necessary testing is gathered (at no cost to the patient), and comprehensive diagnostic work is performed in a short period. A multidisciplinary team then works together to come up with a diagnosis; over time, team members gain valuable information and data on a multitude of rare disorders. The network has been expanded to a national, university-affiliated program in 12 cities, but this is just 1 program that can serve only a minority of the population whose diseases go undiagnosed.

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What Can We Take Home From All This? That Time's a-Wastin'

Imagine that you have gone from physician to physician, from facility to facility, in search of a diagnosis for your or your family member's symptoms—and yet the only impression you leave with after these visits is that you are crazy. You've been given the impression that what you are feeling is just not real, physically and emotionally. Again, you must be crazy.

That situation must change, and quickly. To think that most people with a rare disease go 7 to 9 years without a diagnosis is unacceptable. That is not the kind of care providers envisioned delivering, and it is not why they spent years and years of education so that they could change things.

Education, collaboration, and advocacy are the watchwords. So, how can each of us take part in this diagnostic challenge? Empowering patients and families to be stewards of their health allows for strong and meaningful interactions with every provider. Helping physicians and other providers understand that "rare" does not mean nonexistent is an imperative step to diagnosis.

And after all, if it looks like a zebra and it walks like a zebra, it probably is a zebra.

Rare Epileptic Encephalopathies: Update on Directions in Treatment



Victoria Diep Nguyen
and Quinn Levin

Epileptic encephalopathies are severe neurological disorders that occur in infancy and early childhood. These pediatric epilepsies are characterized by abnormal epileptic electrical discharge; refractory multifocal seizures; increased early mortality; and cognitive, behavioral, and neurological deficits. Early diagnosis and treatment of epileptic encephalopathies are critical for effective management, but are difficult because of the resistant nature of epileptic disorders to antiseizure drugs.

Research is needed to improve care and offer patients who have one of these disorders better quality of life. In this update, we provide a summary of the key features of 3 rare epileptic encephalopathies—West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome—and a synopsis of existing and emerging treatments.

West Syndrome

An age-related disorder, West syndrome was first recognized in 1841 by general medical practitioner William James West, who described spasms in his 4-month-old son.¹ West syndrome is also known as infantile spasms; typically, it is identified in the first year of infancy, with onset between 4 and 7 months of age in 50% to 70% of cases (although the International League Against Epilepsy has described onset of the disorder in children as old as 14 years).² Localization of focal cerebral lesions appears to influence age of onset of West syndrome: 3.4 months for occipital lesions, 6.3 months for centro-temporo-parietal lesions, and 9.8 months for frontal lesions, all following the pattern of functional brain development.³

The incidence of West syndrome is estimated at 1 to 1.6 cases for every 100,000 live births, making it a rare disorder, but the most common type of epileptic encephalopathy.⁴ Despite the relatively low incidence of West syndrome, it is a significant disorder,

considering its association with high mortality, developmental retardation, insensitivity to conventional antiseizure drugs, and unique responsiveness to hormonal therapy.⁵

West syndrome is characterized by spasms usually occurring in clusters, hypsarrhythmia on EEG, and psychomotor regression.⁶ Multiple hypotheses have been put forward to explain a common mechanism for multiple proposed causes of West syndrome, but experts are unsure of the precise pathophysiology; further animal model studies have been recommended to improve understanding of the disorder.⁷ Cases of West syndrome are usually classified as symptomatic (identified cause, 60% to 70% of cases) or cryptogenic (no identified cause); the system of nomenclature is evolving, however, to include an idiopathic group.⁸

Current FDA-approved treatments for West syndrome include adrenocorticotrophic hormone (ACTH) and the antiseizure medication vigabatrin. Although the mechanism of action of ACTH and glucocorticoids is unknown, ACTH has been shown to control spasms in patients with adrenal suppression and is considered the drug of choice for West syndrome.

In 5 randomized, controlled trials comparing ACTH with other therapies, ACTH adequately controlled infantile spasms in 42% to 87% patients with West syndrome, with better response seen in patients with cryptogenic disease than in those with symptomatic disease.⁹ A lower dosage of ACTH produced fewer side effects, including drowsiness and reduced brain size.¹⁰ Two randomized, open-label studies and 2 retrospective case series compared ACTH and vigabatrin, with ACTH showing better spasm control (74% and 48%, respectively).⁹

Despite the therapeutic advantage found for ACTH, vigabatrin is associated with fewer side effects (and is

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especially effective in tuberous sclerosis).¹¹ Furthermore, combined vigabatrin and hormonal therapy was found more effective than hormonal therapy alone. In a multicenter, open-label trial of 377 children with West syndrome, prednisolone (10 mg orally qid) plus vigabatrin (100 mg/kg/day) yielded a higher clinical seizure remission rate than either agent alone and a similar adverse effect profile.¹²

Lennox-Gastaut Syndrome

This syndrome is associated with severe tonic and atypical absence seizures early in childhood that often lead to cognitive dysfunction and developmental delays.¹³ Patients begin presenting with symptoms of Lennox-Gastaut syndrome between 1 and 8 years of age; most cases present between 3 and 5 years.¹⁴ Although Lennox-Gastaut syndrome is inconsistently defined, it is generally diagnosed by the presence of multiple generalized seizure types, a slow (<2.5 Hz) spike-wave pattern (atypical spike and wave) on EEG recordings, and impairment of cognitive function.¹³

Most patients with Lennox-Gastaut syndrome are symptomatic with identifiable causes that include cortical dysplasia, congenital infection, stroke, trauma, perinatal hypoxia, infection of the CNS (encephalitis or meningitis), genetic disorders, and neurocutaneous syndromes (tuberous sclerosis).¹³ Patients presenting with more severe, difficult-to-manage disease often have a history of infantile spasms; these cases constitute 17% to 30% of all Lennox-Gastaut syndrome cases and are associated with poorer prognosis and high mortality.¹⁴ As many as 40% of cases of Lennox-Gastaut syndrome are classified as cryptogenic; these generally present as less severe, with later onset, a milder phenotype, and better cognitive function in adulthood.¹⁵

Genetic factors underlying Lennox-Gastaut syndrome symptoms are not well characterized. However, recent research aimed at identifying genes associated with Lennox-Gastaut syndrome have implicated mutations in *ALG13*, *CHD2*, *DNM1*, *FOXG1*, *GABRB3*, *SCN1A*, *SCN8A*, and *STXBP1* as causative.¹⁶ The long-term outlook for patients with Lennox-Gastaut syndrome with current treatment options is poor; a more comprehensive approach utilizing advances in genetic research is needed for better management of this complicated disorder.¹³

No specific therapy for Lennox-Gastaut syndrome is effective in all cases, and the disorder has proven particularly resistant to most therapeutic options. The three main forms of treatment of Lennox-Gastaut syndrome are antiepileptic drugs, dietary therapy (typically the ketogenic diet) or device/surgery (VNS therapy or corpus callosotomy). Resective surgery is rarely an option.

Valproate is generally considered the first-line drug of choice because it is effective at reducing focal and generalized seizures.¹⁷ Other antiepileptic drug adjunctive therapies, including topiramate, felbamate, lamotrigine, rufinamide, clobazam, and epidiolex, can be considered as subsequent alternatives.¹⁸ These alternatives require further investigation to identify which one is most efficacious for a given patient; treatment should be selected on an individual basis.

Dravet Syndrome

Dravet syndrome, previously known as severe myoclonic epilepsy of infancy, is a rare genetic encephalopathy that begins in the first year of life and affects an estimated 1 in 15,700 people.¹⁵ The major cause of Dravet syndrome is de novo mutations of the sodium channel 1 α gene (*SCN1A*), which is present in approximately 85% of cases.¹⁹ Other genes implicated in the Dravet syndrome phenotype are *PCDH19*, *SCN1B*, *GABRA1*, *STXBP1*, *CHD2*, *SCN2A*, *HCN1*, *KCNA2*, and *GABRG2*.^{20, 21}

People with Dravet syndrome usually present with febrile seizures early, followed by other types of seizures, such as myoclonus and status epilepticus, as the condition progresses.²² The prognosis is poor; there is an increased risk of premature death, usually resulting from sudden unexpected death in epilepsy and status epilepticus.²³

As with other epileptic encephalopathies, patients with Dravet syndrome often display intellectual disability and motor-system abnormalities with age. Genetic testing is critical for early diagnosis, allowing for improved patient outcomes through focused treatment selection, access to adjuvant therapies, and family support networks.

Current treatments are limited; the disorder is highly refractory to antiseizure drugs.²² Most patients with Dravet syndrome require 2 or more drugs to reduce seizures.²⁴ Generally, valproate is considered the first-line medication, followed by addition of clobazam if seizures are still uncontrolled. Valproate is typically dosed at 10-15 mg/kg/day, titrated to a target dose of 25-60 mg/kg/day; this regimen appeared efficacious in multiple studies in Europe and Japan.^{24, 25}

If control of seizures remains suboptimal, stiripentol and topiramate can be considered second-line agents.²² Topiramate might be a reasonable adjunctive treatment for uncontrolled or focal seizures because it has low drug-interaction potential.²² Stiripentol significantly reduced clonic and tonic-clonic seizures when used as add-on therapy to clobazam and valproate; however, the drug is a limited option because it is not readily available in the United States and is available for clinical use only in Canada, Europe, and Japan.²⁶ If first- and second-line treatments prove inadequate for controlling seizures, moderately efficacious options to consider are levetiracetam, clonazepam, and zonisamide.²²

Treatments Under Investigation

West syndrome. Newer antiepileptic medications can be considered in West syndrome, but further study is recommended to confirm that their use is safe and efficacious.²⁷

Valproic acid, zonisamide, topiramate, tiagabine, lamotrigine, and felbamate can be considered as adjunctive therapies in refractory cases.

A modified Atkins diet is another adjunctive therapy to consider for refractory infantile spasms. A prospective study investigated the effectiveness of the diet, in which carbohydrate intake is limited to 10 g/day; several patients were spasm-free after 3 months of treatment.²⁸

The United Kingdom Infantile Spasms Study, which compared the effectiveness of intramuscular synthetic ACTH and high-dosage oral prednisolone, found similar response rates (74% and 70%, respectively). Considering this comparable efficacy, institutions in the United States and Australia have adjusted to utilizing oral prednisolone because of its ease of administration, favorable adverse effect profile, and lower cost. Prednisolone is also being evaluated against vigabatrin as a first-line treatment of West syndrome.¹¹

Last, promising advancements in genetic analysis are being pursued using whole-exome sequencing to help determine novel modifying genes associated with development of West syndrome and evaluate this test's effectiveness as a screening measure to identify ACTH responders.

Lennox-Gastaut syndrome. Medications under investigation for the treatment of LGS are carisbamate and perampanel. Carisbamate is being investigated as a treatment for epilepsy through neuromodulator activity; it has been found effective in tonic-clonic and absence seizures.^{29, 30} Perampanel studies, on the other hand, are investigating this drug's efficacy for drop seizures, also known as drop attacks.³¹ Recently, a prospective study investigated adjunctive therapy, in which notable reduction in seizure frequency was seen with perampanel without major side effects.³²

Dravet syndrome. Fenfluramine, an antiobesity drug, is being investigated as add-on therapy for Dravet syndrome; seizure control with this agent is hypothesized to result from modulation of *N*-methyl-D-aspartate receptor-mediated excitation or through serotonergic effects.³³ Results from previous fenfluramine studies have been significant: namely, a 75% reduction in tonic-clonic seizures, leading to an ongoing phase 3 trial.³⁴

The serotonergic hypothesis has also led to 2 other investigational therapies.³⁵ Trazodone was found to have protective properties against electroconvulsive-induced seizures in mice; researchers believe that it should be further investigated.³⁶ Locaserin was shown to significantly reduce seizure frequency

in patients resistant to at least 5 approved anticonvulsant medications.³⁵

Recently Approved and Emerging Therapies for Dravet Syndrome and Lennox-Gastaut Syndrome

Emerging treatments for these 2 disorders include cannabidiol (CBD); TAK-935, an inhibitor of the enzyme cholesterol 24-hydroxylase; and fenfluramine plus CBD.

The FDA recently approved an oral solution of CBD (trade name, Epidiolex) for patients with Dravet syndrome or Lennox-Gastaut syndrome 2 years of age or older. A recent phase 3 study of CBD for the treatment of seizures associated with Dravet syndrome showed favorable results in reducing the rate of convulsive seizures.³⁷

TAK-935 is an adjunctive therapy under investigation in 2 phase 2 prospective studies to assess long-term safety and tolerability for Dravet syndrome and Lennox-Gastaut syndrome patients.³⁸ Primary end points are efficacy in reducing the frequency of convulsive and drop seizures.³⁸

Fenfluramine and an oral solution of CBD in combination is under investigation for safety and tolerability as adjunctive therapy in patients with Dravet syndrome and Lennox-Gastaut syndrome.³⁹

Promising Future Directions

Although current treatments for West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome are limited, the future is promising for patients suffering from an epileptic encephalopathy. Research is providing a deeper understanding of these complicated disorders, thus creating opportunities for the development of new antiepileptic and hormonal medications.

Advances in genetic sequencing techniques are enabling more rapid diagnosis and having a positive impact on treatment choices that are based on genetic profiles. New opportunities in gene therapy are presenting themselves, with the FDA recently lifting the hold on the first-ever clinical trial of CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein).⁹

These developments not only offer hope for novel therapies, but also build momentum in research for a possible cure and the promise of improved quality of life.

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Are State-by-State Differences in Newborn Screening an Impediment or Asset?



Tim Boyd, MPH

The lifesaving impact of newborn screening (NBS) in the United States is well documented and widely understood among public health experts. Each year, screening identifies thousands of newborns with a disorder that, had it been left undiagnosed and untreated, would have caused severe developmental disability and even death.¹ The immense success of NBS and the rapid growth of promising screening technology have led to increased pressure on states to add conditions to their own screening panels.

Yet not all states do so at the same pace.² This variability in timely adoption of the federal Recommended Uniform Screening Panel (RUSP) is driven primarily by state-to-state discrepancies in managing NBS programs and can be particularly frustrating to patient advocates who know that any delay in screening means lives lost.

As we explain in this article, however, interstate differences in NBS programs can also be a virtue, because of the flexibility offered to individual health departments to design a program that best meets the needs of their residents. Furthermore, states can address gaps in their program and maintain flexibility if NBS receives more support across the board.

Challenges of Operating at the State Level

The need for greater support of NBS screening is well understood among the rare-disease community; all the core conditions included on the RUSP are considered rare. For example, the 4 most recent conditions added to the panel are rare diseases: spinal muscular atrophy (SMA, added in 2018); X-linked adrenoleukodystrophy (X-ALD) and mucopolysaccharidosis type 1 (MPS I) (both in 2015); and Pompe disease (2013).² Each of these conditions causes severe disability and can be fatal when untreated. SMA is the leading genetic cause of death among infants.³

Although the combined impact of effective treatments and population-based screening for rare disorders has been nothing short of transformative, these advancements have also heightened awareness among the broader rare-disease community of the challenges that states face when they want to expand their NBS programs. These challenges, and the frustration among the rare-disease community that comes with them, stem from the pivotal role states play in implementing screening programs. The federal government can only make recommendations to states and incentivize them through grants to screen for certain disorders; the states, on the other hand, are responsible for designing and implementing their programs. This dynamic stems from authority granted to states under the 10th Amendment to the Constitution to protect the public health and welfare.

State discretion over NBS has naturally led to variance around the design and implementation of state programs. Any given state's capacity, including funding, available facilities, and staff capacity, have a great impact on which disorders are included on its screening panel. Only 3 states (Massachusetts*, Minnesota, and New York) screen for all 35 RUSP core conditions.⁴ This gap is driven by the fact that 30 states have not adopted any recent recommendations that call for screening of SMA, MPS I, X-ALD, and Pompe disease. As mentioned, such variability is often of great concern to the rare-disease community.

Tools to Make NBS Programs Work Better

One tool available to states to help fund screening for additional disorders is the fee collected for every initial screen. The amount and use of this fee varies widely from state to state, however. The initial screening fee in Minnesota, for example, is \$150, which is deposited into an NBS-specific program fund; beyond covering the cost of screening, these funds help maintain and

*Massachusetts does not screen for 3 core conditions that are likely still picked up during the screening process.

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improve the state's program capacity. By contrast, Texas has an initial screening fee of \$55 that goes into the general state budget and must be approved for future program uses.⁴

The amount of the NBS fee, and how it is used, do not alone correlate perfectly with whether states can support the addition of new tests for disorders in their program (some states rely on separate legislative appropriations to fund screening). However, states with less flexibility and less funding can struggle to add disorders and ensure proper follow-up of existing conditions.

The authority given to the state agency that implements the NBS program (usually the state health department) also varies from state to state. Although states have broad authority over their screening programs, this power is not always entirely in the hands of health officials tasked with implementing the program. In some states, the health department is unilaterally able to raise the NBS fee and add conditions; in others, health department officials rely on legislative approval or appropriations, or have the support of a designated NBS advisory council.

For states that utilize an advisory council for their NBS programs, this body can be incredibly effective in guiding and overseeing a screening program.⁴ Councils achieve this by bringing together experts in the field and approving program changes that enable the state to make enhancements, including adding new conditions to its program.

To be effective, however, NBS advisory councils must meet and carry out their work in support of the program, especially when council approval is required before any changes can be made. Regrettably, several states are subject to a mandate that the advisory council meet only once a year, not quarterly (or as needed).

Differentiation Isn't Necessarily a Bad Word

Despite these challenges, having differently designed state programs is not inherently an impediment to improving NBS. There are, in fact, aspects of NBS programs that can benefit from differentiation.

To keep pace. Without flexibility, smaller and more rural states with less program capacity could fall further behind national recommendations and standards. For example, Alaska, Hawaii, Idaho, Nevada, New Mexico, and Oregon all participate in the Northwest Regional Screening Program coordinated by the Oregon State Public Health Laboratory.⁵ Regional agencies such as this can not only enhance the capacity of smaller states, but can monitor and improve overall program quality.

To link to services and facilities. Medical follow-up for babies with positive NBS test results must incorporate linkage to existing health facilities. Follow-up procedures in states where multiple major medical universities and children's hospitals

Each year, screening identifies thousands of newborns with a disorder that, had it been left undiagnosed and untreated, would have caused severe developmental disability and even death.

are found might not be suitable in states where there is less capacity. Moreover, certain conditions identified during screening, such as phenylketonuria and other metabolic disorders, are often linked to enrollment in state-specific treatment programs.

To participate in pilot studies. State health departments need flexibility to improve and grow their NBS programs by participating in pilot studies that evaluate new conditions or new testing technologies for implementation. Missouri, for example, recently carried out a pilot study on 4 lysosomal storage disorders intended to assess the effectiveness of a new screening technology for these conditions. Results of this study not only have an immediate benefit on babies whose specimens were identified as positive in the study, but will help improve screening nationwide.⁶

Essential: Strong Support for NBS

Ultimately, difficulties associated with differences in how states implement their NBS programs can only be addressed, and the benefits associated with the differences can only be maintained, if fundamental aspects of the NBS system are better supported. Stakeholders in NBS, including patient groups such as the National Organization for Rare Disorders (NORD), are pushing for changes at the federal and state level to make this support a reality (See "Advocacy at the Federal Level,"^{7,8} next page). State advocates are focused on enhancing program funding by changing policies around setting and collecting the NBS fee, increasing appropriations, reforming state structures (such as advisory councils), and implementing clearer timelines for adoption of the RUSP.

Advocates of NBS Must Press On

Despite the lifesaving success of NBS, continued progress is not guaranteed. Individual citizens, especially parents, are generally enthusiastic about screening once they learn about it, but most people are unaware of how NBS is implemented and what its specific benefits are.⁹⁻¹¹ In addition, increasing concerns over privacy and government overreach have led to anxiety among some communities regarding NBS.¹²

Advocacy at the Federal Level

There is a unique opportunity in 2019 to improve NBS nationally through reauthorization of the Newborn Screening Saves Lives Act (NBSSLA), a critical source of funding for state programs that provides authority and support to the federal Advisory Committee on Heritable Disorders in Newborns and Children that oversees the RUSP. The National Organization for Rare Disorders will join other patient organizations in pushing for changes to this law that would increase funding and enhance support to communities seeking to add a screen for their disease to the RUSP and to states working to improve the quality of their NBS program.

In addition, advocates are seeking to eliminate a provision of current law that has hampered federally funded NBS research.

Nevertheless, advocates for NBS should be encouraged by nascent public support for screening. They should continue to educate their communities on the need to improve state NBS programs.

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Meta-analysis: IVIG Bests Anti-D on Platelet Count in Pediatric ITP

By Will Pass

FROM THE JOURNAL OF PEDIATRICS

For patients with pediatric immune thrombocytopenia (ITP), treatment with intravenous immunoglobulins (IVIG) is more likely to raise platelet count in the short-term, compared with anti-D immunoglobulins (anti-D), according to the authors of a systematic review and meta-analysis.

Although findings from the meta-analysis support recommendations for first-line IVIG, not all studies reported bleeding symptoms, so the clinical effects of differing platelet responses remain unknown, reported lead author Bertrand Lioger, MD, of François-Rabelais University in Tours, France, and his colleagues.

“To date, no meta-analysis has compared the efficacy and safety of IVIG vs. anti-D,” the investigators wrote in *The Journal of Pediatrics*.

Each treatment approach has strengths and weaknesses, the investigators noted. Namely, IVIG is more expensive, while anti-D is more likely to cause adverse drug reactions (ADRs), such as disseminated intravascular coagulation and hemolysis.

The present review evaluated 11 studies comparing the efficacy of IVIG with that of anti-D in 704 children with ITP. Platelet response and bleeding were the main efficacy outcomes. The investigators used response thresholds defined by each study because several did not use standardized levels. Other outcomes considered were mortality, disease course, splenectomy, and ADRs. The ADRs included serious adverse reactions, infusion reactions, transfusions, hemoglobin loss, and hemolysis.

In alignment with previous guidelines, anti-D therapy was most often given to RhD positive, nonsplenectomized children at a dose of 50-75 mcg/kg, whereas IVIG was dosed at 0.8-1 g/kg for 1 or 2 consecutive days.

Results showed that patients treated with IVIG were 15% more likely to have platelet counts greater than $20 \times 10^9/L$ within 24-72 hours, compared with those given anti-D. This disparity rose to 25% in favor of IVIG when using a threshold of $50 \times 10^9/L$.

Treatment risk was lower and general symptoms were less common after treatment with anti-D infusion, compared with IVIG (24.6% vs. 31.4%), but this was only true for trials foregoing premedication. Anti-D was more often associated with hemolysis, making transfusion necessary for some patients.

Although platelet count is often used as a surrogate measure of bleeding risk, the investigators decided that a lack of bleeding data among the studies precluded an accurate determination of clinical superiority between the treatments.

“Severe hemolysis remains an important issue when using anti-D immunoglobulins and premedication reduces the incidence of general symptoms observed with IVIG,” the investigators wrote. “Our conclusions should, however, be cautiously considered due to the poor overall quality of included studies and to limited data about clinically relevant outcomes.”

The study was not supported by outside funding. The investigators reported financial relationships with Amgen, Novartis, Roche Pharma, Sanofi, and others.

SOURCE: Lioger B et al. *J Pediatr*. 2019;204:225-33.

ALL Chemotherapy Looks Effective in Mixed Phenotype Leukemia

By Sharon Worcester



Etan Orgel,
MD

REPORTING FROM ASH 2018

SAN DIEGO—The majority of pediatric patients with mixed phenotype acute leukemia (MPAL) who were treated with acute lymphoblastic leukemia (ALL)–directed chemotherapy achieved a minimum residual disease (MRD)–negative complete response by the end of consolidation, according to findings from a multicenter retrospective cohort study.

The cohort included 94 patients aged 1-21 years who met strict World Health Organization MPAL criteria and were treated between 2008 and 2016 at one of six U.S. institutions. Most had B/myeloid phenotype (89%), and 87 patients were treated with an ALL regimen, Etan Orgel, MD, reported at the annual meeting of the American Society of Hematology.

Of those 87 patients, 81 (93%) experienced an end-of-induction (EOI) complete response. One patient died during induction and six had induction failures, defined as either disease progression before EOI (two patients) or EOI MRD of 5% or greater (three patients), said Dr. Orgel of the University of Southern California, Los Angeles, and Children's Hospital Los Angeles.

The MRD-negative rates, defined as MRD less than 0.01%, were 70% at EOI and 86% at EOI or end of consolidation (EOC); 12 of 14 patients who were MRD positive at EOI and continued on ALL therapy achieved an EOC MRD-negative complete response, including 8 of 8 with EOI MRD of 0.01%-0.09% and 4 of 6 with EOI MRD of 1% or greater.

Event-free survival at 5 years in the 78 patients without hematopoietic stem cell transplant at first remission was 75%, and 5-year overall survival was 89%, "thus demonstrating that, for a majority of patients, transplant in first remission may not be necessary," Dr. Orgel said. "This is very different from the approach used at many adult centers and many of the adult recommendations."

Overall 5-year EOI event-free survival was 80% in the 59 patients who were MRD negative at EOI, and 13% in 25 patients who were MRD-positive at EOI. The corresponding overall survival rates were 91% and 84%.

Overall 5-year EOC event-free survival was 77% in 74 patients who were MRD negative at EOC and was unavailable in 3 patients who were MRD positive at EOC, although all three were salvaged. The corresponding EOC overall survival rates were 89% and "not available," Dr. Orgel reported.

Multivariable analysis confirmed the predictive value of MRD at EOI (hazard ratio for event-free survival and overall survival, 3.77 and 3.54, respectively).

Of note, there was a possible trend toward earlier failure and a trend toward worse overall survival (HR, 4.49, $P = .074$) for T-lineage-containing MPAL.

"That indicates that this might be a group that needs careful scrutiny of which form of ALL therapy they receive," he said.

MRD in pediatric MPAL is rare. Recent studies of MPAL biology show areas of similarity with ALL and AML, and while this could eventually help further subcategorize or classify the disease and lead to biology-driven therapies, it is important to know how to treat the disease today, Dr. Orgel said.

The evolving consensus is that ALL therapy is adequate for most MPAL, but there is no established threshold for MRD to enable a risk-stratified MPAL approach, he added.

The current findings suggest that ALL therapy—without hematopoietic stem cell transplant—may be sufficient to treat most patients with pediatric MPAL, Dr. Orgel reported, noting that clinical trials are necessary to prospectively validate MRD thresholds at EOI and EOC and to establish the threshold for favorable survival.

"Future research should explore either intensification of therapy or different therapies for patients with persistent MRD," he said.

Dr. Orgel reported having no financial disclosures.

SOURCE: Oberley M et al. ASH 2018, Abstract 558.

PKAN Overview and Disease Awareness



Migvis Monduy, MD

Pantothenate kinase-associated neurodegeneration (PKAN)

is a lethal neurodegenerative disorder and the most common type of neurodegeneration with brain iron accumulation (NBIA) disorder. Formerly known as Hallervorden-Spatz syndrome, it is now called NBIA Type I.¹ Historically, it has been divided into classic and atypical forms, depending on age at presentation and symptoms, with an understanding that the disease is a spectrum with overlap between the two subtypes.

Etiology

PKAN is inherited as an autosomal recessive disorder caused by mutations in the pantothenate kinase 2 (*PanK2*) gene located in the 20p12.3-p13 chromosome.² The *PanK2* gene encodes for a mitochondrial enzyme, PANK2, that is responsible for catalyzing the ATP-dependent phosphorylation of dietary pantothenate (vitamin B5) into 4-phosphopantetheinate, the first step in coenzyme A (CoA) biosynthesis.³ CoA is important for a myriad of reactions, including β -oxidation, the citric acid cycle, and fatty acid and amino acid synthesis. The lack of PANK2 enzyme leads to a buildup of substrates in the CoA biosynthetic pathway, including *N*-pantothenyl cysteine and free cysteine. Excessive cysteine can lead to iron accumulation, which in turn results in widespread oxidative damage and cell death. Postmortem studies have shown excess iron deposition and neuronal cell death, particularly in the globus pallidus, in patients with PKAN. It is postulated that *PanK2* mutations ultimately affect energy production and mitochondrial fitness.^{4,5}

The incidence of PKAN is unknown, but it is estimated to affect 1 to 3 per million people (~5,000 people worldwide).⁶ It affects males and females equally. The rate of carrier status is estimated to be 1:275-1:500.

Presentation

PKAN symptoms are highly variable in onset and severity and do not all occur in every patient; therefore, patients may present to different specialists. The hallmark manifestation includes dystonia and parkinsonism. Other symptoms include spasticity, dysarthria, dysphagia, cognitive decline, psychiatric symptoms, and vision problems. Intellectual impairment is typically seen at younger age of onset.⁷ Truncal opisthotonus is common in both classic and atypical forms and is highly suggestive of PKAN.⁶

The subtypes present in the following ways:

Classic PKAN

- Rapid progression of symptoms due to suspected complete absence of pantothenate kinase activity
- Onset before age 6 in most patients
- Clumsy at first and later worsening gait abnormalities
- Frequent falls
- Wheelchair-bound by mid-teens
- Nonambulatory 10 and 15 years after onset of symptoms
- Dysphagia in late teens, may need g-tube by then
- Dystonia is always present and usually an early manifestation
- Bone fractures due to extreme bone stress and osteopenia
- Retinal degeneration
- Optic atrophy⁸
- Risk of premature death, typically related to dysphagia and malnutrition.

Atypical PKAN

- Onset: age 10 to 40
- Slow progression and less severe due to suspected deficiency of pantothenate kinase activity
- Symptom variability

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- Lose ambulation 15 to 40 years after symptom onset
- Speech is affected early on: palilalia, tachylalia, and dysarthria
- Psychiatric symptoms are more common: impulsive behavior, violent outbursts, depression, and rapid mood swings
- Movement problems are common, but develop later: clumsy in childhood and adolescence and later with gait freezing and tremors
- Degeneration of the retina may also occur, though much less often than in classic PKAN.

PKAN is a progressive disorder. Patients experience episodes of rapid deterioration, often lasting one to two months, interspersed with longer periods of stability. The reasons for this are not clearly understood. Patients need medical evaluation when they suddenly worsen to rule out treatable conditions that cause pain (e.g., occult GI bleeding, urinary tract infections, and bone fractures).⁹

Differential Diagnoses

Other disorders to consider include other NBIA disorders, infantile neuroaxonal dystrophy, Batten disease, Tay-Sachs disease, neuroacanthocytosis, Wilson's disease, mitochondrial disease, juvenile Huntington's disease, juvenile Parkinson's disease, Machado Joseph disease (SCA3), and Fahr's syndrome.¹⁰

Diagnosis and Testing

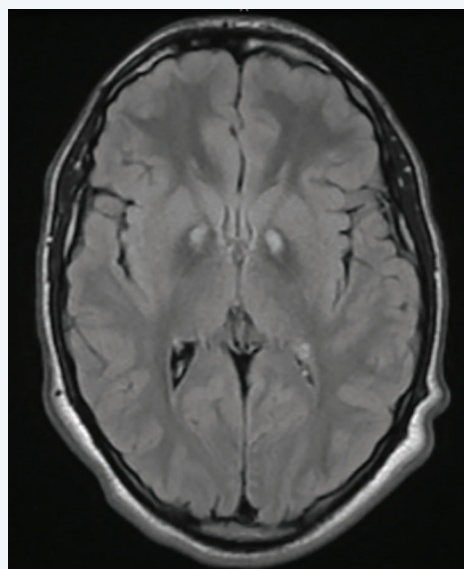
From the history, it is important to elucidate age of onset, progression, associated signs and symptoms, family history of consanguinity, birth history of hypoxia or prematurity, developmental history and regression, and medication and toxin exposure.

The neurologic examination typically finds abnormalities in cognition and speech, cerebellar function, and gait; abnormal movements such as dystonia, rigidity, or choreoathetosis; as well as increased muscle tone and reflexes.

A brain MRI finds "eye of the tiger" sign on T2-weighted images. This sign refers to a central region of hyperintensity surrounded by a rim of hypointensity on coronal or transverse T2-weighted images of the globus pallidus (see Figures 1 and 2). It may be absent in early stages and may be seen in other NBIA disorders.¹¹⁻¹³

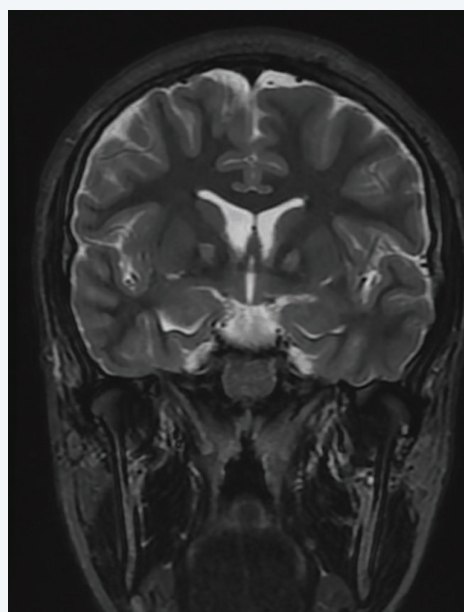
If the index of suspicion is high with typical presentations and abnormal brain MRI, a single gene test (PANK2 gene sequencing with reflex to deletion/duplication studies) will confirm the diagnosis. Sometimes, patients are diagnosed via multi-gene panels (dystonia panels that include *PanK2* gene) or increasingly used comprehensive genomic tests such as Whole Exome Sequencing or Whole Genome Sequencing.

FIGURE 1: Axial FLAIR image showing eye of the tiger.



Courtesy of Migvis Monduy, MD

FIGURE 2: Coronal T2 image showing eye of the tiger.



Courtesy of Migvis Monduy, MD

Treatment

There are no disease-specific treatments approved. Supportive treatment is symptom-specific and involves multiple disciplines including neurology or movement disorders specialists; physical, speech, and occupational therapists; psychologists; psychiatrists; GI/nutritionists; orthopedists; physiatrists; ophthalmologists; genetic counselors; and dentists for extractions for severe oromandibular dystonia. Feeding should be monitored by a feeding therapist. Initially, diet modification may be all that is needed, but as the disease progresses and patients develop dysphagia, a feeding tube may be recommended. A low-iron diet is not recommended, as it will lead to systemic iron deficiency without impacting brain iron accumulation.

Dystonia is typically the most debilitating and distressing symptom. Oral medications such as baclofen, trihexyphenidyl, benzodiazepines, tetrabenazine, and gabapentin are used.¹⁴ For focal dystonias, botulinum toxin injections are appropriate.¹⁵ Surgical options include ablative pallidotomy or thalamotomy, intrathecal baclofen pump, and deep brain stimulation.^{16, 17} With advancing disease, patients may exhibit status dystonicus/dystonic storm with severe, continuous dystonia that can be associated with tachycardia, hypertension, cardiac arrhythmias, rhabdomyolysis, and acute renal failure. It is important to rule out other medical causes (e.g., pain, infection, constipation, fracture) and treat accordingly.⁹ Supportive treatment with ICU admission for IV continuous muscle relaxants (e.g., benzodiazepines) and paralytics with concurrent airway protection or intubation is often needed until dystonia can be controlled.

The role of iron chelation is still unclear. Early agents were ineffective and caused iron deficiency anemia. Deferiprone, a newer agent, was investigated in an international phase III clinical trial; the agent was well tolerated, reduced iron in the basal ganglia, and slowed disease progression at 18 months, although not significantly. An 18-month extension trial confirmed these findings. Pantothenate (vitamin B5) and pantothenate derivatives may help atypical PKAN patients with some possible partial enzyme by increasing substrate with high-dose pantothenate (vitamin B5). Clinical studies are underway.

Summary

PKAN is a lethal neurodegenerative disorder and the most common type of NBIA disorder. It is diagnosed based on clinical presentation and eye of the tiger sign on MRI. Genetic testing confirms the diagnosis. As disease-specific treatments may soon become available, it is important to recognize and promptly diagnose this disorder.

RESOURCES

NBIA Disorders Association
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Email: info@nbiadisorders.org
www.nbiadisorders.org

NBIA Alliance
Email: info@NBIAalliance.org
www.nbiaalliance.org

For information about clinical trials conducted in the US,
www.clinicaltrials.gov

For information about clinical trials conducted in Europe,
www.clinicaltrialsregister.eu

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Gene-Based Therapy for Rare Pediatric Neuromuscular Disorders Puts Transition-of-Care Issues in the Spotlight



Vamshi K. Rao, MD

Rare diseases are defined as conditions that affect fewer than 200,000 people at any given time. One in 10 people in the United States, 350 million people worldwide, are affected by a rare disorder. There are more people affected with a rare disease in the United States than with human immunodeficiency virus infection, heart disease, and stroke *combined*. Furthermore, approximately 50% of people affected by a rare disease are children, 30% of whom die before their fifth birthday.¹

Although 95% of rare disorders do not have a US Food and Drug Administration-approved treatment, there has been welcome progress in research. This has led to 1) approved treatments for spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD) and 2) encouraging news that a clinical trial is underway for a treatment for X-linked myotubular myopathy (XLMTM).

This article describes important advancements in the treatment of those 3 rare pediatric neuromuscular disorders. We then consider how the welcome fact of the increasing longevity and better health of these patients will challenge medicine's and society's ability to 1) provide a smooth transition from pediatric to adult care and 2) adapt milestone legal and lifestyle events that will come as a consequence of longer life.

Overview: Spinal Muscular Atrophy

In its most common form, SMA is caused by a homozygous deletion of the *SMN1* gene. The disorder has a prevalence of approximately 1 to 2 for every 100,000 people and an incidence of 1 in every 10,000 live births. Type 1 SMA accounts for approxi-

mately 60% of cases²; in the past, infants born with this type could not achieve sitting and died before their second birthday.

Successful clinical trials led to the first treatment for SMA approved in the US in 2016. Nusinersen, trade name Spinraza, is an antisense oligonucleotide that increases full-length protein production from *SMN2* (a paralog of the homozygously deleted *SMN1*). The drug was safe and well-tolerated without serious adverse effects related to treatment.

Analysis of efficacy demonstrated class-I evidence for term infants with SMA and 2 copies of *SMN2*, showing that treatment with nusinersen started at younger than 7 months of age results in a better motor milestone achievement and a higher rate of event-free survival than was seen in control subjects. There is also class-I evidence that nusinersen-treated children 2 to 12 years of age with symptom onset after 6 months of age had greater improvement in motor function at 15 months compared with controls.

There is class-III evidence that nusinersen improves the probability of permanent ventilation-free survival at 2 years of age for infants with homozygous *SMN1* deletions or mutations, compared with appropriate natural history cohorts.³

These exciting developments are coupled with promising therapeutics based on other approaches, such as gene replacement, neuroprotection, and increasing signaling across the neuromuscular junction, to name a few.

Overview: Duchenne Muscular Dystrophy

Estimated to occur at a frequency of 1 in every 3,500 live male births, DMD usually has symptom onset between 3 and

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5 years of age.^{4,5} The disorder is an X-linked progressive disease caused by the dystrophin gene, in which affected children start losing muscle function early, leading to wheelchair dependency at approximately 12 years of age, need for assisted ventilation around 20 years of age, and premature death in the third or fourth decade of life. In addition to skeletal muscle involvement, there is progressive cardiac dysfunction.

Dystrophin is a large gene containing 79 exons, ripe with the potential for mutations in multiple locations, leading to disease. Mutations amenable to exon 51-skipping were targeted in clinical trials initially, as they constituted 13% to 14% of all patients.

In 2016, the FDA approved eteplirsen, trade name Exondys 51, for treating DMD, making it the first approved drug for this disorder. The current clinical trial landscape for DMD looks promising: Multiple strategies are being studied, including, but not limited to, exon skipping, dystrophin gene transfer, anti-inflammatory therapies, enhancing muscle growth and force of contraction, mitochondrial regulation, and improving cardiac function.

Overview: X-Linked Myotubular Myopathy

A rare monogenic disease, XLMTM is caused by mutations in the *MTM1* gene and is typified by severe muscle weakness, respiratory failure, and premature death. Recently, the incidence of XLMTM has been shown to be 1 in every 40,000 live male births. Approximately 50% of affected children die by 18 months to 2 years of age; for children who survive this period, the chance of 10-year survival is 75% to 80%.⁶

On the therapeutic front, the experimental agent AT132 was devised as a product in which the functional *MTM1* gene is inserted in an adeno-associated virus 8 vector. Preclinical studies in animal models of XLMTM demonstrated that single administration of AT132 resulted in improvement of motor function and survival. There were no serious treatment-related adverse events.

Human clinical trials of AT132 were carefully devised, and an interim analysis of data, reported at the World Muscle Society in October 2018, revealed that treatment provided to 8 enrolled patients for 4 to 48 weeks showed encouraging safety and efficacy trends. These included incremental motor achievements that resulted in improvements in neuromuscular and respiratory function. All 7 treated patients in the first cohort had a significant reduction in ventilator use, 3 of whom achieved ventilator independence. Muscle biopsy at Week 24 showed efficient tissue transduction and robust protein expression.⁷

Well-studied retrospective charts and prospective natural history studies have shown that there is a larger prevalent population of older affected boys who might benefit from treatment with AT132 even though they are severely functionally impaired.

Forewarning of a “Chasm of Care” Developing

As we celebrate the successes of nusinersen for SMA and eteplirsen in DMD and of the encouraging results of AT132 for XLMTM, and look forward to the arrival of other gene-based therapies for these and other rare disorders, we need to consider the emergence of a potential chasm in care. Current interventions, as well as ones proposed for the future, are causing welcome shifts in the natural history of rare diseases. These changes were coming to the fore even before the arrival of gene-based treatments, with improvements in evolving guidelines for standards of care—changes that resulted in natural history studies of SMA and DMD that revealed improved quality of life and survival.⁸⁻¹⁰

Improving and evolving guidelines for standards of care, coupled now with approved treatments, will further extend survival, challenging existing systems of transition care. More people with a rare disorder will be able to seek higher education, but will also face harsh realities of the scarcity of meaningful employment. Social exchanges largely driven by parents may be easier and richer, in most cases, in the pediatric years, whereas social isolation could be a possibility in personal relationships later in life. Although treatments for these diseases are promising, we are not at the point of certain cure; because the possibility of adverse events leading to progression and irreversibility always exists, end-of-life decisions can become both a legal and ethical consideration for these patients.

To complicate matters, alterations needed with all the above possibilities will vary by type and stage of disease. Furthermore, the needs of a person living longer and reaching adulthood will force our systems to adapt or modify centers of education, places of employment, and living situations to cater to those who need further education and work and seek a family life of their own.

The Transition of Care

Transition care as a solution, although well-recognized, has long been known to be riddled with complexities because of the extraordinary needs of a person with an underlying disorder and to a lack of infrastructure and systematic flow. Barriers to successful transition are varied; they include 1) child neurologists who are not confident that their adult counterparts have the training to address the needs of adults with a childhood-onset disorder and 2) adult neurologists having to struggle with an unprepared and unwilling patient who has expectations that have never been modified by the child neurologist.¹¹⁻¹³ At the heart of the matter seems to lie the scenario of a patient shifting from a model centered on family-driven care to a model in which care is patient-driven.

Although transition care can be intimidating and overwhelming, effective models that bring together the health care community can prevent crises that stem from a lack of a medical home, medication refills, and responsible providers to direct treatment. Additionally, the participation of educational and vocational institutions will further ensure higher education and meaningful employment for these people.

Principles proposed in 2014 by the Child Neurology Foundation to tackle transition of care provide an effective launching pad.¹⁴ The Foundation's consensus statement was also endorsed by the American Academy of Neurology, the Child Neurology Society, and the American Academy of Pediatrics in 2015. The proposal calls for:

- **discussing transition expectations** at 13 years of age
- **annual assessments of self-management skills** starting at 12 years
- **transition planning and transfer readiness** to be discussed at dedicated transition appointments at 13 years
- **discussing legal competency** at 14 years and, if unclear, reevaluating annually
- **ensuring that a multidisciplinary transition plan is crafted** to address health care, finances, legal issues, employment, housing, and other matters
- **making annual updates to the transition plan**, including health care issues, goals for adult treatment, and planned timing of transition to an adult neurologist
- **identifying an adult provider** before the expected time of transfer; if such a provider is not identified before time of transfer, the child neurology team should continue to provide adequate interim care
- **communicating with the chosen adult provider** to ensure transfer has been made and care established, with direct access for consultation should the need arise.

A bold move beyond these proposed guidelines would be to recommend that transition care be made a sub-discipline, in which a "transition care-trained physician" on the pediatric and adult sides would help streamline the transfer.

To Summarize

Changes that have come about secondary to both improved guidelines for the standard of care and the development of promising treatments for rare diseases will ensure improved survival and quality of life. In turn, however, such changes could expose a void in care as a result of changing phenotypes of genetic disorders, neuromuscular and otherwise.

Phenotypic and genotypic homogeneity are deliberate considerations in clinical trials and are required to demonstrate

a meaningful change with the interventions in question. Upon approval, these drugs might carry a wider label, allowing for treatment of a much more heterogeneous population, resulting in potentially multiple phenotypes. This increase in phenotypic and possibly genetic variability, along with increased survival of children and adults with a rare disorder, will stress the need for constantly evolving standard of care guidelines that align somewhat with the principles of precision medicine.

The seeming dichotomy—the need for multidisciplinary management balanced against the specific needs of an individual who has a rare disorder—will eventually melt away. Furthermore, an ensuing continuum of care will allow for seamless transition of care from childhood to adulthood.

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Angelman Syndrome Treatment Safe, Well-tolerated, and Effective in Exploratory Analyses

By Andrew D. Bowser

REPORTING FROM AAN 2019

PHILADELPHIA—OV101 (gaboxadol), a type A gamma-aminobutyric acid receptor agonist, was safe, well-tolerated, and improved clinical outcomes in a phase 2 trial of adults and adolescents with Angelman syndrome, according to results of a study presented at the annual meeting of the American Academy of Neurology.

Clinician-rated clinical global impressions of improvement (CGI-I) were improved versus placebo in the randomized study, as were other outcomes in post hoc analyses, including measures of sleep and motor function, said Alexander Kolevzon, MD, professor of psychiatry and pediatrics at the Icahn School of Medicine at Mount Sinai, New York.

This study of OV101 was a genetics-driven trial for the rare genetic disorder, which is caused by mutations in UBE3A and characterized by seizures, speech impairments, profound intellectual disability, gait problems, and anxiety, Dr. Kolevzon said in a press conference.

"The only treatments that exist are really very symptomatically driven," Dr. Kolevzon said. "Here, we are taking a genetics-first approach. Having identified the gene, there is some understanding of what the underlying biology is, and it seems to relate to deficits in tonic inhibition."

OV101 is a delta-selective type A gamma-aminobutyric acid receptor agonist that may potentially normalize the tonic inhibition that is decreased in Angelman syndrome. "What we think this compound is doing is actually reversing the

deficits of tonic inhibition, and sort of restoring that state to these patients," Dr. Kolevzon said in the press conference.

A total of 78 patients completed the phase 2, randomized study, known as STARS, which had a primary endpoint of safety and tolerability over 12 weeks of treatment with OV101 once daily, twice daily, or placebo. The mean age of the 87 patients who enrolled and had at least one dose of study drug was 22.6 years.

Most adverse events were mild, and frequencies of specific adverse events were similar for OV101 and placebo treatment groups, according to Dr. Kolevzon and his coinvestigators.

Improvements in motor function, sleep, and behavior were seen in a series of exploratory analyses, including global improvement at week 12, as captured by CGI-I, which was significantly improved for daily OV101 versus placebo ($P = .0006$).

These phase 2 results have informed discussions of which specific endpoints might be incorporated into the design of a planned phase 3 trial in pediatric patients. The CGI-I may be especially useful to measure clinical improvement in Angelman syndrome, which is a very "heterogeneous" disorder, Dr. Kolevzon said in the press conference.

"Every child has a different composite of symptoms, so that is the big challenge," Dr. Kolevzon said. "I do not think we are going to have one singular outcome. The idea is to have a global measure that really captures heterogeneity across each trial and allows for children to be compared to their baseline, and each as their own control, in essence, but with specific domains in mind."

Funding for the study came from Ovid Therapeutics. Dr. Kolevzon reported disclosures related to Ovid Therapeutics, as well as Coronis Neurosciences, 5AM Ventures, SEMA4, LabCorp, and AMO Pharma.

Neurodevelopmental Concerns May Emerge Later in Zika-exposed Infants

By Tara Haelle



Sarah Mulkey,
MD

REPORTING FROM PAS 2019

BALTIMORE—Most infants prenatally exposed to Zika showed relatively normal neurodevelopment if their fetal MRI and birth head circumference were normal, but others with similarly initial normal measures appeared to struggle with social cognition and mobility as they got older, according to a study.

“I think we need to be cautious with saying that these children are normal when these normal-appearing children may not be doing as well as we think,” lead author Sarah Mulkey, MD, of Children’s National Health System and George Washington University, Washington, said in an interview. “While most children are showing fairly normal development, there are some children who are ... becoming more abnormal over time.”

Dr. Mulkey shared her findings at the Pediatric Academic Societies annual meeting. She and her colleagues had previously published a prospective study of 82 Zika-exposed infants’ fetal brain MRIs. In their study, they followed up with the 78 Colombian infants from that study whose fetal neuroimaging and birth head circumstance had been normal.

The researchers used the Alberta Infant Motor Scale (AIMS) and the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA) to evaluate 72 of the children, 34 of whom underwent assessment twice. Forty of the children were an average 5.7 months old when evaluated, and 66 were an average 13.5 months old.

As the children got older, their overall WIDEA z-score and their subscores in the social cognition domain and especially in the mobility domain trended downward. Three of the children had AIMS scores two standard deviations below normal, but the rest fell within the normal range.

Their WIDEA communication z-score hovered relatively close to the norm, but self-care also showed a very slight slope downward, albeit not as substantially as in the social cognition and mobility domains.

The younger a child is, the fewer skills they generally show related to neurocognitive development, Dr. Mulkey explained. But as they grow older and are expected to show more skills, it becomes more apparent where gaps and delays might exist.

“We can see that there are a lot of kids doing well, but some of these kids certainly are not,” she said. “Until children have a long time to develop, you really can’t see these changes unless you follow them long-term.”

The researchers also looked separately at a subgroup of 19 children (26%) whose cranial ultrasounds showed mild nonspecific findings. These findings – such as lenticulostriate vasculopathy, choroid plexus cysts, subependymal cysts and calcifications – do not usually indicate any problems, but they appeared in a quarter of this population, considerably more than the approximately 5% typically seen in the general population, Dr. Mulkey said.

Though the findings did not reach significance, infants in this subgroup tended to have a lower WIDEA mobility z-scores ($P = .054$) and lower AIMS scores ($P = .26$) than the Zika-exposed infants with normal cranial ultrasounds.

“Mild nonspecific cranial ultrasound findings may represent a mild injury” related to exposure to their mother’s Zika infection during pregnancy, the researchers suggested. “It may be a risk factor for the lower mobility outcome,” Dr. Mulkey said.

The researchers hope to continue later follow-ups as the children age.

The research was funded by the Thrasher Research Fund. Dr. Mulkey had no conflicts of interest.

Lentiviral Gene Therapy Appears Effective in X-CGD



Donald B.
Kohn, MD

By Andrew D. Bowser

REPORTING FROM TCT 2019

HOUSTON—Lentiviral gene therapy appears safe and was potentially effective in a rare primary immunodeficiency disease known as X-linked chronic granulomatous disease, said Donald B. Kohn, MD, of the University of California, Los Angeles.

Seven of nine patients treated were “alive and well” at 12 months’ follow-up after receiving lentiviral vector transduced CD34+ cells, Dr. Kohn reported in a late-breaking clinical trial session at the Transplantation & Cellular Therapy Meetings.

Most patients were able to discontinue antibiotic prophylaxis for this disease, which is associated with severe, recurrent, and prolonged life-threatening infections, he said.

Results of the small study provide “proof of concept” for use of the gene therapy in the disease, though additional studies are needed to formally assess the clinical safety and efficacy of the approach, he said.

Results of the small study provide “proof of concept” for use of the gene therapy in the disease, though additional studies are needed to formally assess clinical safety.

The estimated incidence of chronic granulomatous disease is 1 in 200,000 births in the United States, and the X-linked form is most common, occurring in about 60% of patients, Dr. Kohn told attendees of the meeting held by the American Society for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research.

Most of these patients are treated with antibacterial or antifungal prophylaxis. While allogeneic hematopoietic stem cell transplantation is also an option, according to Dr. Kohn, the approach is limited by a lack of matched donors and graft-versus-host disease.

Dr. Kohn reported results for nine patients in the United States and the United Kingdom who were treated with the same G1XCGD lentiviral vector. The patients, who ranged in age from 2 to 27 years, underwent CD34+ cell mobilization or bone marrow isolation, transduction with the lentiviral vector, busulfan conditioning, and autologous transplantation.

All patients had confirmed X-linked chronic granulomatous disease, and had had at least one severe infection or inflammatory complication requiring hospitalization.

There were no infusion-related adverse events, and one serious adverse event, which was an inflammatory syndrome that resolved with steroids. Two patients died from complications unrelated to gene therapy, Dr. Kohn reported.

“The other patients are basically doing quite well,” he said.

Of the seven patients alive at the 12-month follow up, six were reported as “clinically well” and off antibiotic prophylaxis, according to Dr. Kohn, while the seventh patient was clinically well and receiving antimicrobial support.

Dr. Kohn is a scientific advisory board member for Orchard Therapeutics, which licensed the lentiviral gene therapy for X-CGD discussed in his presentation. He is also an inventor of intellectual property related to the therapy that UCLA has licensed to Orchard.

At its meeting, the American Society for Blood and Marrow Transplantation announced a new name for the society: American Society for Transplantation and Cellular Therapy (ASTCT).

SOURCE: Kohn DB et al. TCT 2019, Abstract LBA1.

An Overview of Moebius Syndrome: Diagnosis, Supportive Treatment, and Valuable Community Resources



Bryn D. Webb, MD, and Vicki McCarrell

Moebius syndrome was first described by German ophthalmologist Alfred Graefe in 1880, but is named for German neurologist Paul Julius Moebius, who reported cases of this condition in 1888 and 1892.¹⁻³ Varying descriptions of Moebius syndrome have since been reported in the medical literature, and there have been major differences in opinion regarding the necessary key features for a diagnosis of this condition.

Diagnostic Criteria Plus Associated Findings

To improve consistency in diagnosis, minimum diagnostic criteria for a diagnosis of Moebius syndrome were established by an international group of experts at a Moebius Syndrome Foundation research conference in 2007. Minimum diagnostic criteria are the following:

- congenital, nonprogressive facial weakness
- inability to abduct (move the eye away from the nose) one or both eyes.

Both criteria must be present to make a diagnosis of Moebius syndrome (Figure 1).^{4,5}

Keep in mind that congenital facial weakness can occur secondary to a defect in the facial nucleus or cranial nerve 7, and therefore might be a neurogenic problem. The term *congenital facial paresis* refers to decreased facial nerve function; *congenital facial paralysis* refers to absent facial nerve function.

Clinical characteristics of facial weakness can include facial droop; absence of forehead, nasolabial, or periorbital folds; lagophthalmos (incomplete eyelid closure), open-mouthed posture or U-shaped upper lip; drooling; and inability to make

FIGURE 1: Congenital facial weakness

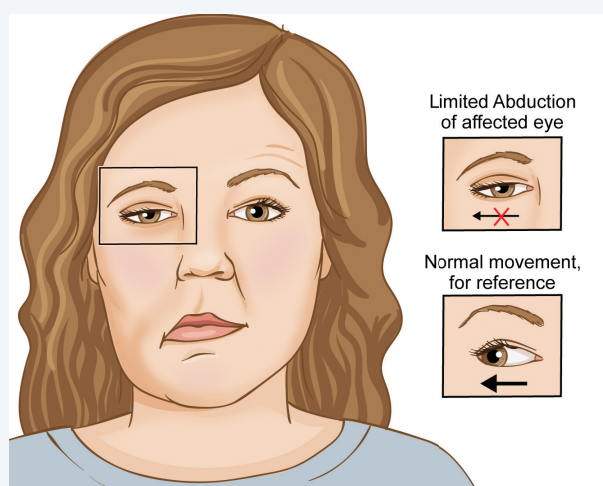


Illustration by Jill K. Gregory, CMI.
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facial expressions (such as smiling), wrinkle the forehead, or whistle. A defect in the abducens nucleus or cranial nerve 6 can result in failure to abduct the eye, due to impaired ability to contract the lateral rectus extraocular muscle.

In addition to the 2 above-mentioned minimum diagnostic criteria, other signs or symptoms might be present, but are not necessary, in persons with Moebius syndrome (Table 1).

Dr. Webb, a member of the board of directors of the Moebius Syndrome Foundation, is Assistant Professor of Genetics and Genomic Sciences and Pediatrics, Icahn School of Medicine at Mount Sinai Hospital, New York, New York; she is also Codirector of the Cleft and Craniofacial Clinic at Mount Sinai Hospital. Vicki McCarrell is President of the Moebius Syndrome Foundation.

This article is the work of the Moebius Syndrome Foundation.

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TABLE 1. Moebius syndrome: Diagnostic criteria, other signs and symptoms

Minimum required diagnostic criteria

Congenital, nonprogressive facial weakness
Inability to abduct (move the eye away from the nose) either or both eyes

Additional signs and symptoms*

Autism
Congenital heart disease
Developmental delay or intellectual disability
Hearing loss
Limb-reduction defects
Muscular hypotonia
Poland anomaly (underdevelopment of the pectoralis major chest muscle, often with ipsilateral syndactyly)
Strabismus (misalignment of the eyes)
Talipes equinovarus (clubfoot)
Other cranial-nerve involvement
Other limb anomalies.

*Not required for diagnosis; not found in every patient. Not an exhaustive list.

The incidence of Moebius syndrome is roughly 2 to 20 cases in every 1 million births. The condition occurs in all ethnicities. There is no gender bias: males and females are affected equally.

The etiology of Moebius syndrome is poorly understood; the syndrome might be caused by genetic or environmental factors, or both. Prenatal exposure to misoprostol or cocaine has been associated with a Moebius syndrome phenotype, suggesting that vasoconstriction in the developing hindbrain or diminished or interrupted blood flow might be a cause.^{6,7} In very rare cases, in patients affected with congenital facial weakness and a variety of additional findings, *de novo* heterozygous mutations in *PLXND1* or *REV3L* have been identified.⁸

In addition, there are several other separate conditions with similarities to Moebius syndrome that have identified genetic causes. These include hereditary congenital facial palsy, *TUBB3* syndrome, Carey-Fineman-Ziter syndrome, and CHARGE syndrome (coloboma of the eye; heart defects; atresia of the nasal choanae; retardation of growth or development, or both; genital and/or urinary abnormalities; and ear abnormalities and deafness).

Multidisciplinary Supportive Care Is Needed

There is no specific cure or treatment for Moebius syndrome. Treatment is supportive and aimed at treating symptoms of the condition individually. Comprehensive care and a multidisciplinary approach are needed to optimize patient health and clinical outcomes. Patients are often treated by a primary care physician, neurologist, ophthalmologist, otolaryngologist,

medical geneticist, plastic surgeon, speech therapist, dentist, psychologist, or other specialists.

Infants with Moebius syndrome often have feeding difficulties; they might benefit from the use of special bottles, such as the Haberman feeder, and may require a feeding tube for additional nutritional support. Respiratory support is sometimes also needed. Speech and physical therapies are often recommended from an early age, with the aim of improving swallowing and feeding, speaking, and motor skills and coordination. School-aged children and adults might benefit from specialized oral-motor exercises to improve awareness and sensation of particular facial muscles, and might aid in strengthening facial movement.

Facial reanimation surgery (so-called smile surgery) is often an option to improve facial movement. Aims of this surgery include enabling the patient to smile, achieving symmetry, reducing pronunciation difficulties or swallowing problems, and improving dental health. Techniques vary, and include gracilis muscle transfer with use of the masseteric nerve or a cross-facial nerve graft, temporalis tendon transfer, and lengthening temporalis myoplasty. Eye surgeries, such as tarsorrhaphy or gold weights, may be recommended to prevent corneal exposure.

Additional surgeries might be recommended, based on the individual patient's symptoms, including for strabismus, limb anomalies, and scoliosis.

Foundation Support Has Been Essential and Effective

In 1994, the Moebius Syndrome Foundation (MSF) was launched as the first national patient advocacy organization for patients and families affected by Moebius syndrome. The organization was formed after 2 women, Vicki McCarrell and Lori Thomas, whose children were affected with Moebius syndrome, met and noted that few resources were available for those with Moebius syndrome. The first MSF conference was held in 1994 in Los Angeles.

Over the years, the foundation has grown tremendously and now has more than 2,800 members. Detailed information about the foundation can be found at www.moebiussyndrome.org. The mission of the MSF is to provide information and support to people with Moebius syndrome and their families, promote greater awareness and understanding of Moebius syndrome, and advocate for scientific research to advance the diagnosis and treatment of Moebius syndrome and associated conditions.

To fulfill this mission, the MSF hosts a large, 4-day family and scientific conference every other year in the United States. The conference has an international presence; at the last conference, held in the summer of 2018 in St. Petersburg, Florida, there were 410 attendees for the family conference and 50 investigators in attendance for the scientific conference. Sessions at the

family conference covered such topics as smile surgery, hand surgery techniques, speech and feeding therapies, treatment for sleep disorders, psychological issues, and an overview of Moebius syndrome research. Social events at the conference included a highly attended talent show and dance party.

The 2020 Moebius Syndrome Foundation Conference will be held in Minneapolis, Minnesota, July 17-19, 2020.

New Resources in 2019

The MSF is also initiating a mini-conference series to enable additional networking within the Moebius syndrome community. Mini-conferences will include a full-day schedule of events and will be held twice yearly in the United States.

The MSF hosts a large, 4-day family and scientific conference every other year in the United States. The 2020 Moebius Syndrome Foundation Conference will be held in Minneapolis, Minnesota, on July 17-19, 2020.

Additionally, the MSF hosts a closed Facebook group, "The Home for the Moebius Community," to enable additional networking within the Moebius syndrome community. This active group has 534 members.

The MSF also has supported scientific research on Moebius syndrome since 2005. Funding priorities include the following:

- projects that advance the diagnosis, treatment, or quality of life of people with Moebius syndrome and associated conditions

- projects that promote sustainable and comprehensive programs of research focused on Moebius syndrome by providing seed funds for larger research programs and grant submissions to larger funding organizations.

The MSF research grant program encourages early-career and established investigators to apply for funding. Researchers can learn more about these opportunities at www.moebiusssyndrome.org. To date, the MSF has provided nearly \$900,000 in research support.

The MSF also interacts with other global Moebius syndrome foundations to increase awareness of Moebius syndrome as well as share information and resources with physicians and individuals and families affected by Moebius syndrome. The MSF is also proud to be one of the initial members of Face Equality International, headquartered in England, and founded in 2018. This alliance of nongovernmental organizations works to "improve the life prospects of any person anywhere in the world who has a facial difference or disfigurement, an unusual-looking, scarred or asymmetrical face."

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Rare Diseases Aren't as Rare as You Might Think: Look to the NIH's Many Resources for Help



Tiina K. Urv, PhD, and
Anne R. Pariser, MD

Rare diseases aren't rare. That statement might sound contradictory: After all, a rare disease is defined (in the United States) as a disease or condition of fewer than 200,000 affected persons living in the United States. Collectively, however, there are approximately 7,000 different rare diseases, with about 250 newly identified conditions added to the list each year. That equates to approximately 30 million Americans who are affected by a rare disease—more than the number of people who have cancer, human immunodeficiency virus infection, and Alzheimer's disease combined, and nearly as many as the number who have diabetes (Figure 1).

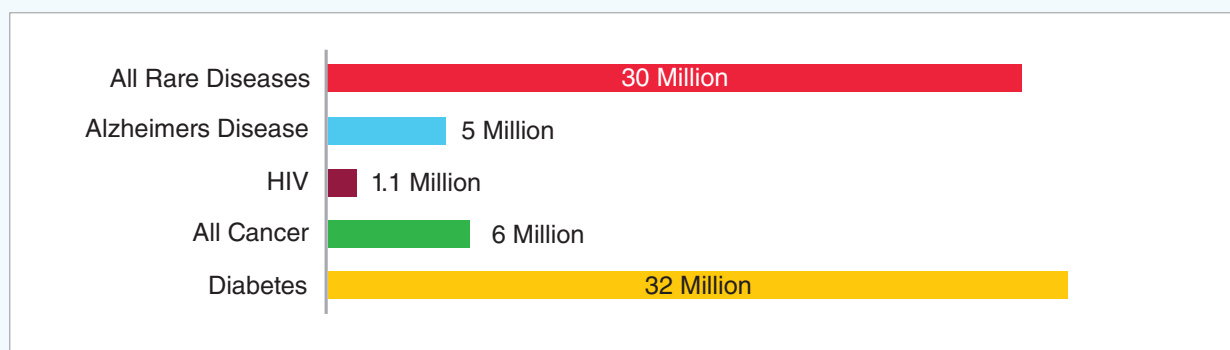
More than one half of the 30 million people affected by a rare disease in the United States are children. Most rare diseases are serious and can involve chronic illness, disability, and, often, premature death. Rare diseases are complex, and treat-

ments exist for fewer than 5% of these conditions. It is important, therefore, to recognize that rare diseases are a significant public health issue. And since 350 million people are affected by rare diseases worldwide, it is not just a national problem, but a global problem.

One of the greatest challenges facing people who have a rare disease is getting an accurate and timely diagnosis. The average time from onset of symptoms to diagnosis is 4.8 years (range, 0-20 years), during which time these people visit approximately 7 physicians, on average.¹ It is understandable why this process is often referred to as the diagnostic odyssey.

Since 1 in 10 Americans is affected with a rare disease, it is highly likely that during the course of any given day, a physician will encounter a patient with a rare disease in the

FIGURE 1: Estimated prevalence of rare and other selected diseases



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This article reflects the views of the authors and should not be construed to represent the views or policies of NCATS or NIH.

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TABLE 1. Rare Diseases Clinical Research Network Consortia

Autonomic Disorders Consortium (ADC) https://rdcrn.org/adc	NEPTUNE: Nephrotic Syndrome Study Network https://rdcrn.org/neptune
Brain Vascular Malformation Consortium (BVMC) https://rdcrn.org/bvmc	North American Mitochondrial Disease Consortium (NAMDC) https://rdcrn.org/namdc
Brittle Bone Disorders (BBD) https://rdcrn.org/bbd	Porphyrias Consortium (PC) https://rdcrn.org/porphyrias
Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) https://rdcrn.org/cegir	Primary Immune Deficiency Treatment Consortium (PIDTC) https://rdcrn.org/pidtc
CReATe: Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium https://rdcrn.org/create	Rare Kidney Stone Consortium (RKSC) https://rdcrn.org/rksc
Developmental Synaptopathies Consortium (DSC) https://rdcrn.org/dsc	Rare Lung Diseases Consortium (RLDC) https://rdcrn.org/rlc
Dystonia Coalition https://rdcrn.org/dystonia	Rett Syndrome, MECP2 Duplication, & Rett-Related Disorders Consortium (RTT) https://rdcrn.org/rett
Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) https://rdcrn.org/gdmcc	STAIR: Sterol and Isoprenoid Research Consortium https://rdcrn.org/stair
Inherited Neuropathies Consortium (INC) https://rdcrn.org/inc	Urea Cycle Disorders Consortium (UCDC) https://rdcrn.org/ucdc
Lysosomal Disease Network (LDN) https://rdcrn.org/ldn	Vasculitis Clinical Research Consortium (VCRC) https://rdcrn.org/vcrc

examining room. This situation raises a question: How could a single physician be expected to have knowledge of more than 7,000 disorders that he has never encountered? During training, medical students have historically been taught that when you are working up a patient to make a diagnosis and you hear hoofbeats (i.e., see symptoms), you should look for horses, not for zebras—meaning that a common diagnosis is much more likely than an unusual one.

Many providers and researchers in the rare disease community have adopted the zebra as their mascot: They are the uncommon cause of hoofbeats in the medical field. Physicians, in this age of rapidly advancing science, might find themselves contending with not 1, but a herd of zebras, and it can be challenging to know where to turn for reliable information about rare diseases.

One Good Place to Turn

The National Institutes of Health (NIH) (www.nih.gov), part of the US Department of Health and Human Services, is the

nation's medical research agency. Among many other services, the NIH conducts and supports research related to rare diseases—from the most basic bench research to translational, clinical, and broad overall public health research.

The NIH comprises 27 institutes and centers (<https://www.nih.gov/about-nih/what-we-do/nih-almanac/nih-organization>), many of which conduct rare disease research. It can be daunting to know where within such a large institution to find information related to rare diseases. The answer? Within the National Center for Advancing Translational Science (NCATS) (<https://ncats.nih.gov>) of the NIH resides the Office of Rare Diseases Research (ORDR) (<https://ncats.nih.gov/about/center/org/ordr>).

The ORDR was established at the NIH in 1985 (originally as the Office of Rare Diseases). The ORDR supports programs that help accelerate scientific discovery and offers patients and their health care providers information on identifying, diagnosing, treating, and living with a rare disease. The office does so by facilitating coordination among

multiple stakeholders in the rare disease community, including scientists, clinicians, patients, and patient groups.

In 2002, Congress and President George W. Bush further established the ORDR and its responsibilities in a statute by enacting the Rare Diseases Act of 2002. The ORDR has established numerous resources for researchers, patients, and clinicians, which we catalogue and describe in this article.

NCATS ORDR Programs for Rare Diseases Genetic and Rare Diseases Information Center (GARD)

<https://rarediseases.info.nih.gov>

GARD is a collaboration of the National Human Genome Research Institute and NCATS/ORDR to provide comprehensive information about rare and genetic disease to patients, their families, health-care providers, researchers, and the public. Use of the GARD website and Contact Center is broad and has continued to grow (Figure 2).

The GARD website and database provide comprehensive, reliable, plain-language information on rare or genetic diseases that is freely accessible to the public and available in English and Spanish. Videos, brochures, publications, and links to disease-related organizations are also available. A contact center staffed by information specialists with expertise in genetic counseling provides free, individualized responses by telephone or email to support patients with a rare disease.

Rare Diseases Clinical Research Network (RDCRN)

<https://www.rarediseasesnetwork.org>

The RDCRN was established by the Rare Diseases Act of 2002 as the Rare Diseases Clinical Research Centers of Excellence. The RDCRN comprises a number of consortia, each studying at

least 3 disorders and partnering closely with patient advocacy groups and NIH program staff (Table 1). The goal of the network, through its consortia, is to advance the diagnosis, management, and treatment of rare diseases. Each consortium promotes highly collaborative, multisite, patient-centric translational and clinical research. The individual consortia and the RDCRN are supported by a data management and coordinating center.

The network was first funded in 2003 and has been funded continuously since that time, with a recompetition every 5 years. To date, the program has successfully supported 31 individual consortia that have conducted research on 238 disorders, involving more than 40,000 participants, all leading to a greater understanding of rare diseases.

The aims of the upcoming program are to specifically address, through clinical research, 5 challenges to bringing effective treatment to more people living with rare diseases.

Making a diagnosis can be challenging. Many patients experience a diagnostic odyssey of many months, even years, because of limited knowledge of the range of disease manifestations and of genotype-phenotype studies.

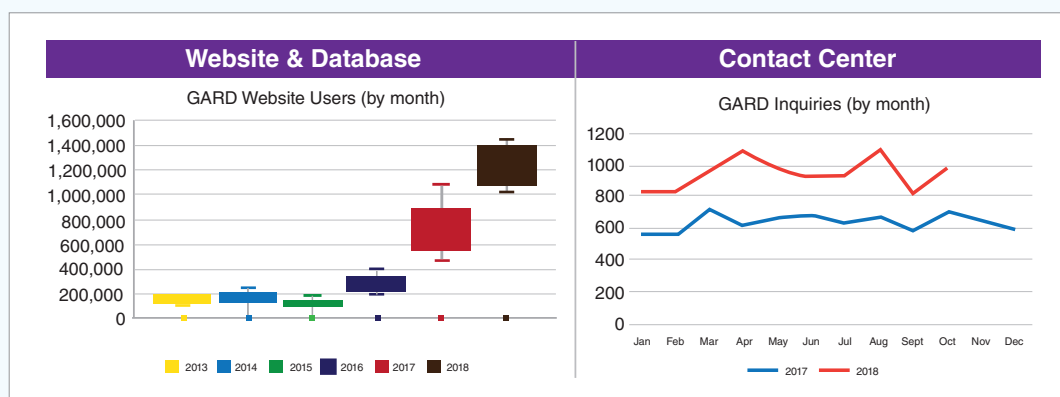
Often, there are no high-quality natural history data sets documenting how a disease affects patients' functioning and how it progresses over time.

Often, there are no adequate clinical or biological markers to support the clinical development of new therapeutics

The number of patients and clinicians caring for them is relatively small, leading to challenges in the design and implementation of clinical trials.

Resources for developing therapeutics are limited, making it critical to find frameworks for leveraging partnerships among patient groups, industry, academic investigators,

FIGURE 2: Genetic and Rare Diseases Information Center (GARD) utilization in recent years



and federal funding agencies. In addition, the global burden associated with rare diseases necessitates international coordination and collaboration.

The RDCRN is a partnership of multiple NIH Institutes and Centers, including NCATS; the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute of Allergy and Infectious Diseases; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the Eunice Kennedy Shriver National Institute of Child Health and Human Development; the National Institute of Dental and Craniofacial Research; the National Institute of Diabetes and Digestive and Kidney Diseases; and the National Institute of Neurological Disorders and Stroke.

An important component of the RDCRN is the Coalition of Patient Advocacy Groups (CPAG). This collective representation of patient groups is affiliated with the consortia within the RDCRN. The mission of CPAG is to promote collaboration between rare disease advocacy organizations and the RDCRN to facilitate better access to and earlier benefit from research conducted on rare diseases. As the patient advocacy arm of the RDCRN, CPAG members use their position to advance rare disease research and improve patient outcomes through the network. There are 151 active member patient organizations participating in the CPAG.

NCATS Toolkit for Patient-Focused Therapy Development <https://rarediseases.info.nih.gov/toolkit>

The toolkit was developed by ORDR in collaboration with patient groups and is intended to provide patient groups with the tools needed to help advance their research agenda. It provides a single site that draws accessible, practical, action-centered information from many groups across the Internet. The goal of the program is to ensure that patients are engaged as essential partners from beginning to end of research and development. This is a living site to which tools are continually being added for and by patient groups in concert with their academic, government, industry, and advocacy partners. An example of a tool within the kit is a description of how a new therapy for a disorder is developed (<https://rarediseases.info.nih.gov/toolkit/getting-started>).

Rare Diseases Registry Program (RaDaR) <https://rarediseases.info.nih.gov/radar>

The Rare Diseases Registry Program (RaDaR) is a component of the toolkit that is under development and expected to be released in 2019. This program is not a registry, but a tool to develop a registry. Registries and natural history studies are the foundations of any drug development program, especially for rare diseases. They provide information about the rare disease,

establish a link to patients, aid in the identification and development of outcome measures, contribute to the interpretability of clinical studies, and serve as a comparator group in trials. Information collected in a registry has to meet specific needs to be used in research.

The intent of RaDaR is to be a “registry in a box.” It will connect researchers and patient groups to tools with training and instruction on key decisions, tasks, and challenges needed for creating and managing a registry. When complete, RaDaR will provide step-by-step directions for creating high-quality registries to support clinical trials and therapy development. It will provide templates and tools to incorporate best practices and standards for registries, along with strategies for maintaining, promoting, using, and expanding registries.

NIH Resources Beyond the ORDR

The Undiagnosed Diseases Network

<https://undiagnosed.hms.harvard.edu>

The Undiagnosed Diseases Network (UDN) was established to meet the needs of the hundreds of men, women, and children who face uncertainty when their providers are unable to discover the cause of their symptoms. The UDN provides information for patients and families affected by mysterious conditions and helps them learn more about common diseases. The goals of the network are the following:

- **improve the level of diagnosis and care** for patients with undiagnosed diseases, through development of common protocols designed by a large community of investigators.
- **facilitate research into the etiology of undiagnosed diseases** by collecting and sharing standardized, high-quality clinical and laboratory data, including genotyping, phenotyping, and documentation of environmental exposures.
- **create an integrated and collaborative community** across multiple clinical sites and among laboratory and clinical investigators prepared to investigate the pathophysiology of these new and rare diseases.

The program consists of clinical sites across the United States (Table 2) and supporting cores related to DNA sequencing, metabolomics, and model organisms. Because of the complex nature of the human body and the diseases being investigated, the UDN cannot accept all applicants into the study. However, all applications receive full review. To date, 2,939 applications have been submitted; 1,215 have been accepted into the program; 952 participants have been evaluated; and 249 have been given a diagnosis.

This program is funded by the NIH Common Fund (<https://commonfund.nih.gov>). Physicians and patients can refer themselves; however, a study recommendation letter is

TABLE 2. Clinical sites of the Undiagnosed Diseases Network (UDN)

Bethesda, Maryland (National Institutes of Health)
Boston, Massachusetts (Brigham and Women's Hospital, Boston Children's Hospital, and Massachusetts General Hospital)
Durham, North Carolina (Duke University and Columbia University)
Houston, Texas (Baylor College of Medicine)
Los Angeles, California (University of California, Los Angeles)
Miami, Florida (University of Miami School of Medicine)
Nashville, Tennessee (Vanderbilt University Medical Center)
Philadelphia, Pennsylvania (Children's Hospital of Philadelphia and University of Pennsylvania)
Salt Lake City, Utah (University of Utah)
Seattle, Washington (University of Washington School of Medicine and Seattle Children's Hospital)
Stanford, California (Stanford Medicine)
St. Louis, Missouri (Washington University in St. Louis)

needed from a licensed primary health care provider. To be eligible for the UDN program, a participant must:

- have a condition that remains undiagnosed despite thorough evaluation by a provider
- have at least 1 objective finding
- agree to the storage and sharing of information and biomaterials in an identified fashion amongst the UDN centers, and in a deidentified fashion to research sites beyond the network (<https://undiagnosed.hms.harvard.edu/apply>).

Educational Materials About Genetics and Genomics

<https://www.genome.gov/education>

Approximately 80% of rare diseases adhere to Mendelian laws of inheritance, and genomic science and technology are fast-moving. To continually educate the public and health-care professionals, the National Human Genome Research Institute has developed extensive materials and online genetic education resources, as well as online courses related to genomics and genetics.

Clinicaltrials.gov

<https://clinicaltrials.gov/ct2/home>

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. This web-based resource, provided by the National Library of Medicine, provides patients and their family members, health care professionals, researchers, and the public with easy access to information on clinical trials on a range of diseases and conditions. The site allows users to find and view clinical studies, learn more about clinical research, manage study records, and use site tools and data.

Research Portfolio Online Reporting Tools (RePORT)

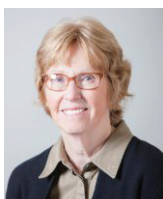
<https://report.nih.gov/index.aspx>

The Research Portfolio Online Reporting Tool provides a central point of access to reports, data, and analyses of NIH research activities, including expenditures and results of NIH-supported research. A tool that is exceptionally valuable in finding information about specific rare diseases is the NIH RePORTER tool (<https://projectreporter.nih.gov/reporter.cfm>), which allows members of the public to search for research related to any disease or disorder. Using a simple, web-based query, information regarding ongoing research projects, publications, patents, and clinical studies can be accessed, along with data visualization and the NIH institute that is funding the research.

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NORD Offers Resources to Benefit Health Care Providers, Patients, and Caregivers



Mary Dunkle

The National Organization for Rare Disorders (NORD) (<https://rarediseases.org>) has been providing resources for health care providers since 1983. As the primary nonprofit organization representing patients and families affected by rare diseases in the United States, NORD considers support for health care providers to be an essential part of its mission.

An informed and supported medical care team is one of the most important assets that patients and caregivers coping with a rare disease can have. As a result, NORD sees outreach to health care providers as one of the foundations of its services for patients and caregivers.

NORD resources for health care providers can be found within each of the 4 pillars of NORD programs and services: education, advocacy, patient and family services, and research.

1. Education

NORD's Rare Disease Database (<https://rarediseases.org/for-patients-and-families/information-resources/rare-disease-information/>) is a unique and widely cited resource that encompasses expert-reviewed, disease-specific reports providing overviews of approximately 1,200 rare diseases.¹ These reports include general descriptions, synonyms and subdivisions, signs and symptoms, causes, affected populations, related disorders, standard therapies, investigational therapies, resources (including disease-specific patient organizations), and references.

Of the approximately 1 million visits to NORD's website each month, 85% first go to the Rare Disease Database. Medical experts assist NORD in developing the reports and serve as reviewers to ensure accuracy. In many cases, the reviewers are the physicians for whom the diseases are named, or who serve as the world's leading experts on their topic. These medical experts volunteer their time and

support because of the value of the database in educating other providers and students, as well as affected patients and caregivers.

NORD recently obtained permission from the National Institutes of Health (NIH) to display information from the NIH **Genetic and Rare Diseases Information Center (GARD)** (<https://rarediseases.info.nih.gov/>) alongside NORD's disease information on the NORD website. These combined resources cover all 7,000-plus known rare diseases.

In addition to the database of disease reports, NORD maintains a database of more than **1,000 patient organizations** (<https://rarediseases.org/for-patients-and-families/connect-others/find-patient-organization/>) that provide services for people affected by rare diseases. This database can be searched by disease or organization name. Many patient organizations in this database provide services helpful to providers, including information about genetic testing, centers of excellence, and consultation and telemedicine services.

NORD will soon launch its **Rare Disease Video Library**, which will include short (approximately 4-minute) animated videos providing overviews of rare diseases. These videos cover information similar to what is in the Rare Disease Database reports, but in an engaging format for providers as well as patients and caregivers. The videos will be available on the NORD website.

The monthly **NORD eNews** digital newsletter reaches a broad audience, including many health care providers. It covers upcoming conferences and events, funding opportunities, advocacy initiatives, news from NIH and the Food and Drug Administration (FDA), including recently approved drugs for rare disorders, and other topics of interest to providers caring for patients who have rare diseases.

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In 2019, NORD expects to launch a **Continuing Medical Education (CME) program** that will include a mix of live events and online access-on-demand resources. NORD hosted its first CME event in 2017 and has been building on that experience to develop an expanded program to meet the needs of community physicians, RNs, PAs, and others serving as members of the health care team for patients affected by rare diseases.

The annual NORD Rare Diseases and Orphan Products Breakthrough Summit (www.nordsummit.org/) takes place each October in Washington, DC, and addresses cutting-edge topics related to rare diseases. The 2018 Summit was the largest to date, with more than 800 participants, including NIH and FDA staff, clinicians, researchers, patient organization leaders, and industry representatives. With a mix of general and breakout sessions, topics in 2019 include drug pricing, gene therapy, social determinants of health, and patient registries.

NORD also hosts conferences for patients, caregivers, students, and providers at locations around the United States. The 2020 Living Rare, Living Stronger Forum will be held in Cleveland, Ohio in May 2020.

NORD provides **educational resources for patients and caregivers** about current topics related to rare diseases that can be helpful to members of the care team. NORD hosts a webinar series for patients and caregivers on topics such as “Genetic Testing 101” and “How to Make Your Insurance Work for You.” Some of NORD’s webinars are also geared to providers, such as a recent session on “Emergency Protocols” and guidelines for responding to patients with rare diseases in emergency situations.

In its **Patient/Caregiver Resource Center**, (<https://rare-diseases.org/for-patients-and-families/information-resources/patient-and-caregiver-resource-center/>) NORD provides links to videos and free downloadable resources. A recently created video, “Patient/Caregiver Questions About Gene Therapy,” has been widely viewed and circulated among patients, caregivers, and providers. Another video provides an overview of resources for patients whose rare disease is newly diagnosed.

For **Rare Disease Day** (www.rarediseaseday.us), observed globally on the last day of February each year, NORD provides special resources and news about events of interest to providers, patients, and caregivers.

2. Advocacy

Through its office in Washington, DC, and a network of state and local volunteers known as the **Rare Action Network®** (<https://rareaction.org/>), NORD leads advocacy on state and federal public policy issues that affect the rare disease community. These initiatives include advocating for:

- funding for medical research
- patient access to affordable health insurance
- coverage for medical foods and newborn screening
- patient protections around the use of step therapy and related practices.

Over the years, NORD has played a major role in advocacy to encourage development of diagnostics and treatments for people with rare diseases, to end discrimination against those with pre-existing medical conditions, and to support expanded funding for rare disease research at the NIH.

3. Patient and Family Services

Since 1987, NORD has provided assistance programs (<https://rarediseases.org/for-patients-and-families/help-access-medications/patient-assistance-programs-2/>) to help patients obtain life-saving and life-sustaining medical and other resources that they could not otherwise afford. These programs provide medication, financial assistance with insurance premiums and co-pays, diagnostic testing assistance, and travel assistance for clinical trials or consultation with disease specialists.

NORD’s **Patient Services** staff provides white-glove service to patients and caregivers, working closely with physicians and physicians’ office staff to ensure that patients have access to the medical care their providers believe is best for them.

4. Research

NORD and Critical Path Institute launched the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) through funding from the FDA. The Platform is an integrated database and analytics hub that is designed to be used in building novel tools to accelerate drug development across rare diseases by pulling in patient-level data from diverse sources, including clinical trials, longitudinal observational studies, patient registries and real-world data (eg, electronic health records) across a multitude of rare diseases.

This year marks the 30th anniversary of NORD’s **Research Grants Program** (<https://rarediseases.org/for-clinicians-and-researchers/research-opportunities/research-grant-program/>), which provides grants—typically \$30,000 to \$50,000, sometimes greater—for the study of rare diseases. The intent is to advance understanding of specific rare diseases and provide funding for studies that might lead to new diagnostic tools or treatments for patients.

In at least 2 cases, research that was initially funded by a NORD seed grant led to a product approved by the FDA:

- The so-called titanium rib, approved in 2004 through FDA’s Humanitarian Use Device pathway, was developed by

researchers at Santa Rosa Children's Hospital, San Antonio, Texas, for children affected with any of several rare disorders resulting in thoracic insufficiency syndrome (<https://news.uthscsa.edu/titanium-rib-becomes-1st-new-fda-approved-spine-deformity-treatment-in-40-years/>). This medical device has been credited with saving the lives of hundreds of children over the years.

- A drug for neurogenic orthostatic hypotension, approved by FDA in 2014, resulted from research that began with a grant from the NORD Research Grants Program (<https://www.drugs.com/history/northera.html>).

NORD grants are competitive and international. The intent is to support the most promising research that has the

As the primary nonprofit organization representing patients and families affected by rare diseases in the United States, NORD considers support for health care providers to be an essential part of its mission.

greatest likelihood of improving the lives of patients. Each year, funding opportunities are posted on the NORD website, usually in late winter or early spring.

Letters of intent and final proposals are reviewed by the NORD Medical Advisory Committee, whose members are rare disease experts at teaching hospitals and medical schools across the United States. Members of this committee volunteer their time to make it possible for NORD to offer this program.

Grants are funded by donations from patients, family and friends of patients, patient organizations, foundations, and other sources. Anyone can make a donation to NORD for this purpose, and if no fund exists for a specific disease, a new one can be started. Typically, NORD has active funds for more than 200 rare diseases. When a fund reaches the required minimal amount, a Request for Proposals (<https://rarediseases.org/for-clinicians-and-researchers/research-opportunities/requests-proposals/>) will be generated.

Program guidelines and policies are available on the NORD website. When new requests for proposals are posted, NORD advertises them through its eNews, on its website, and through disease-specific patient organizations. The intent is to cast the broadest possible net to get the best possible proposals.

In recent years, NORD has also launched a **platform for patient registries and natural history studies** to advance understanding of rare diseases and support research. NORD works with disease-specific patient organizations to develop global registries that are tailored to the needs of each patient community.

NORD is currently hosting or developing 29 registries, working with organizations such as the Foundation for Prader-Willi Research, the OMSLife (Opsoclonus Myoclonus Syndrome) Foundation, the Fibrous Dysplasia Foundation, and the Platelet Disorder Support Association. These organizations are encouraged to interact with medical researchers and look for opportunities to collaborate for the benefit of the patient community.

Resources of NORD Member Organizations

In addition to NORD's own resources, those developed by its **nearly 300 member organizations** (<https://rarediseases.org/for-patient-organizations/membership-profiles/member-list/>) are also often featured on the NORD website or through its communications media.

For example, **CureSMA**, which represents families affected by spinal muscular atrophy (SMA), recently launched a new **SMart Moves** microsite (<http://events.curesma.org/site/PageNavigator/SmartMoves/SmartMoves.html>) and campaign to help parents and providers recognize early signs and symptoms of SMA. Early identification of infants affected by SMA is extremely important because treatment is available that, begun early, can greatly improve quality of life and, for some patients, slow the advance of this progressive condition.

NORD helps its member organizations promote awareness of these types of resources to educate patients and providers about specific rare diseases.

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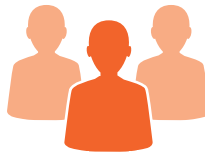
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COMMITTED TO THE IDENTIFICATION, TREATMENT AND CURE OF RARE DISEASES

The National Organization for Rare Disorders® is leading the fight to improve the lives of rare disease patients and families. We work together with the rare community to accelerate research, raise awareness, provide valuable information and drive public policy that benefits the over 25 million Americans impacted by rare diseases.



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Madilyn (left) has been battling a rare breathing disorder since birth called Congenital Central Hypoventilation Syndrome (CCHS), or Ondine's Curse.

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and help drive innovation
for rare diseases.**



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Alone we are rare. Together we are strong.®