Pediatric Rare Dx

A PCP Primer to Diagnosing Rare Disease

Created by the National Organization for Rare Disorders (NORD®) Rare Disease Centers of Excellence

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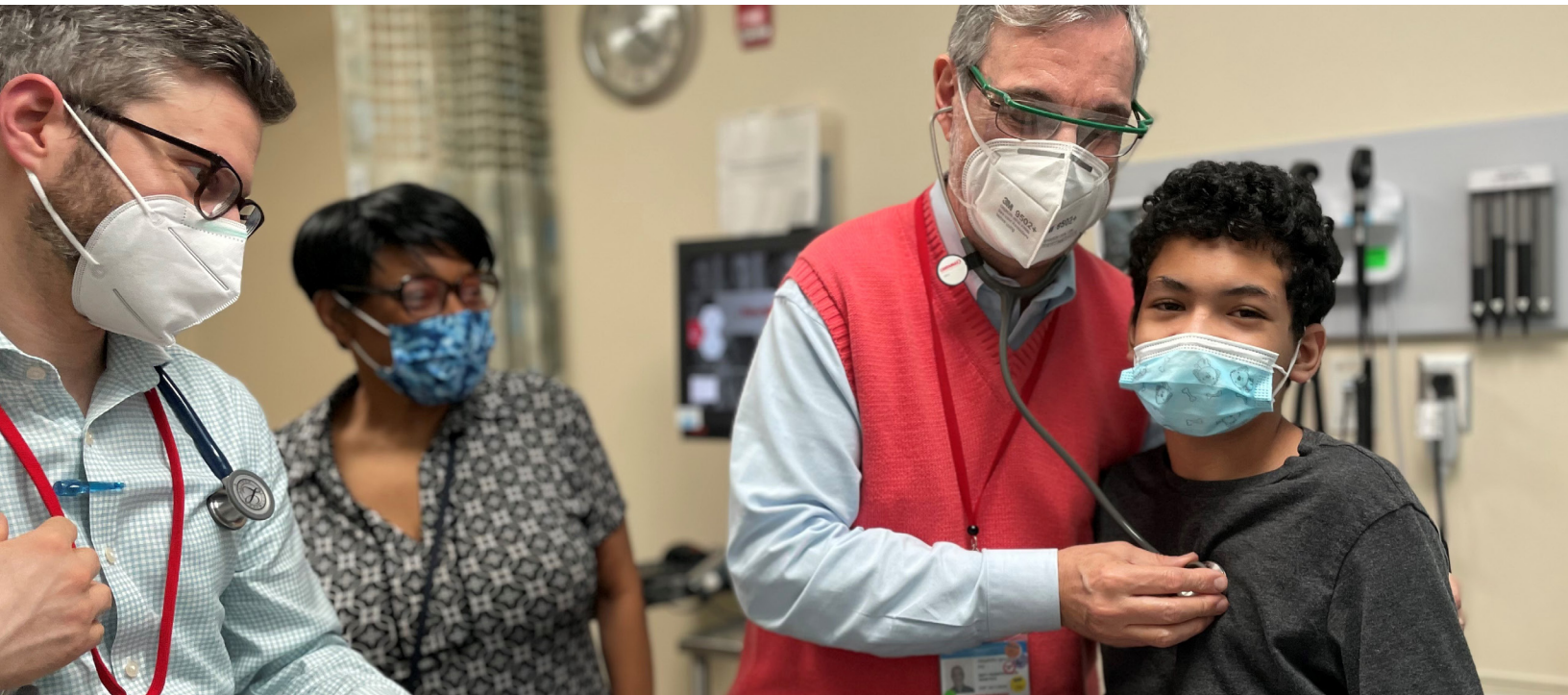

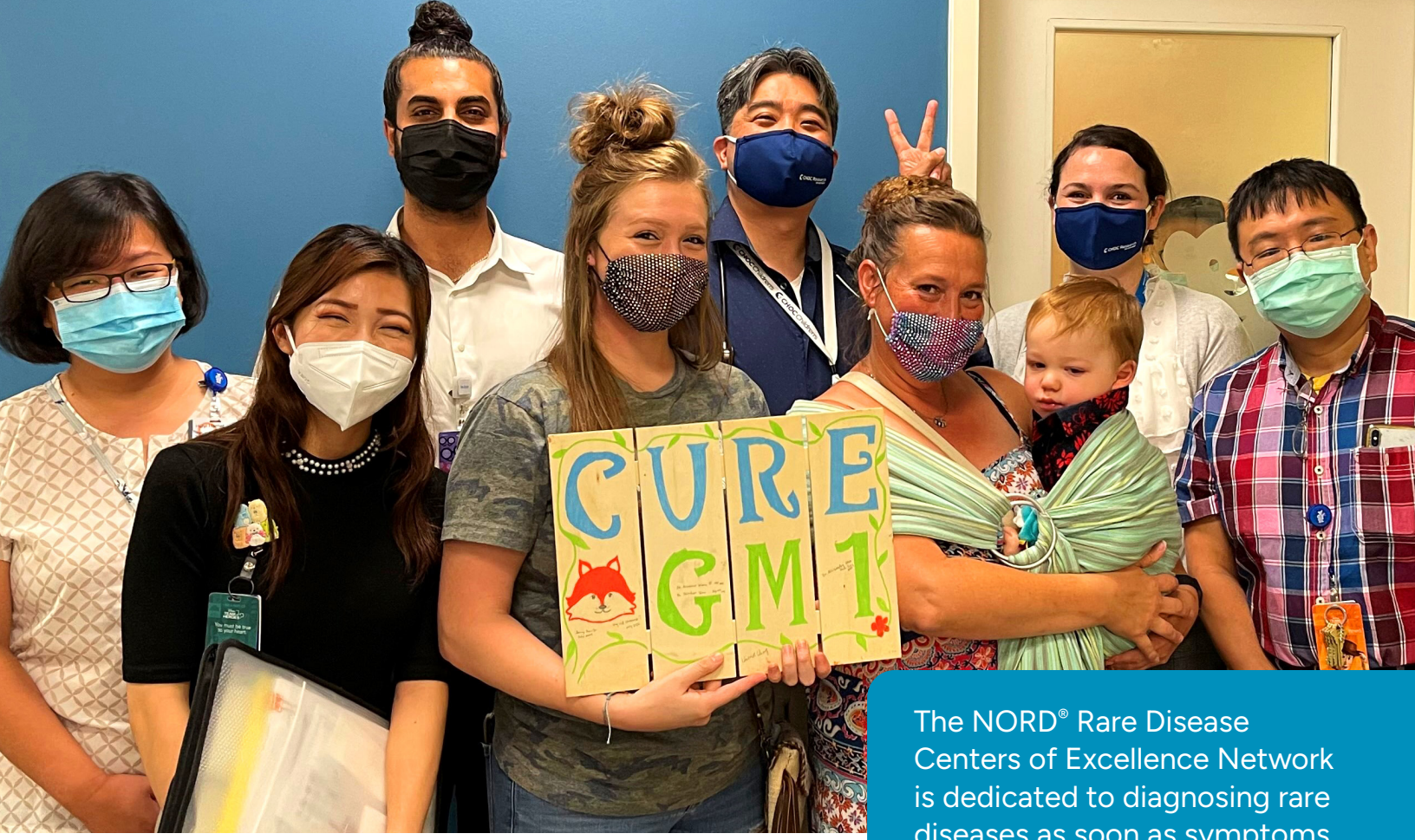

The NORD® Rare Disease Centers of Excellence Network is dedicated to diagnosing rare diseases as soon as symptoms appear, while also advancing research to make an accurate diagnosis faster.

Rare Diseases and the Diagnostic Odyssey

In the United States, rare diseases are defined as medical conditions affecting fewer than 200,000 people. Over 30 million Americans, or **close to 1 in 10**, are living with a rare disease. Approximately 80% of these rare diseases either have, or are strongly suspected to have, a genetic cause, and **over half affect children**.

Families facing the possibility of a rare disease may find themselves on a diagnostic odyssey, a journey that typically begins when a child experiences unexplained symptoms, continues as the child is evaluated by their primary care provider (PCP), and then in most circumstances, by additional specialists. The journey ends when a final diagnosis is made. The diagnostic odyssey can last months, years, or even decades. Currently, not all rare diseases can be diagnosed, but many can, and as medical science advances, more children with rare diseases will be diagnosed.

The NORD® Rare Disease Centers of Excellence Program aims to diagnose children who have a rare disease as early as possible after symptoms begin and advance science so more rare diseases can be diagnosed.

This guide has been prepared by a working group of physicians, genetic counselors, genetic laboratory directors, and researchers at NORD Rare Disease Centers of Excellence to help pediatric PCPs like you guide your patients and their families through the diagnostic odyssey. This group has also prepared a separate guide to help parents and caregivers better understand the diagnostic pathway and how to partner with their child's PCP to accelerate a diagnosis (Pediatric Rare Dx: A Parent's Guide to a Rare Disease Diagnosis).

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Could my patient have a rare disease?

PCPs play a critical role in the diagnostic odyssey as they are often the first clinician to interact with a patient when symptoms arise. As a PCP, you may come across situations where your patient's concerns do not appear to match up with diseases that you have encountered before. Recognizing when a particular symptom or sign might indicate a rare disease can be challenging.

Sometimes pathognomonic findings or an established family history may allow a clear path to diagnosis, but often symptoms can be subtle, slowly evolving, multisystem, and complex, or can mimic more common diseases. Some features that may indicate a rare disease include:

Functional or anatomic concerns on fetal ultrasound

Congenital anomalies

Medical problems affecting more than one part of the body

Abnormal newborn screening results

Differences in growth, such as growing too slowly or too quickly, or one part of the body growing out of proportion to the rest

Developmental delays or regression

Social or behavioral differences such as autism

Seizures, especially if unprovoked, frequent, or difficult to control

Health problems that begin early in life or that continue to get worse

Illnesses that are excessively frequent, severe, or prolonged, or that do not respond to treatment as expected

Family history of similar unexplained symptoms

Recurrent episodes of hypoglycemia or acidosis, particularly if happening without a clear cause

Recurrent episodes of encephalopathy or ataxia

Other times, it may not be specific features that suggest the possibility of a rare disease but rather an overall feeling or impression. In these circumstances, if careful evaluation suggests that your patient's symptoms are not caused by an atypical presentation of a more common disorder, the combined consequences of several common disorders, or the side effects of medications, other therapies, or environmental or infectious exposures, then your patient may have a rare disease. **As a rule of thumb, when you and one or more appropriate specialists are unable to make a specific diagnosis after two or more evaluations, your patient may have a rare disease.**

The critical role of the primary care provider

PCPs like you play a critical role in the early detection of rare diseases in children. This includes:

- Documenting the child's medical history and phenotype
- Initiating specialist referrals
- Coordinating ongoing, multi-disciplinary care

As the main point of contact, you ensure continuity throughout the diagnostic process, facilitating timely access to tests and evaluations. **Your comprehensive involvement can help shorten the path to diagnosis and ensure the child receives appropriate care early in the onset of symptoms.**

TAKE ACTION

Certain presentations benefit from a consistent approach to referral. For example, referral to a clinical geneticist for a genetic evaluation should be considered for children with seizures and brain malformations, as well as for children with growth and cognitive developmental delays. The American College of Medical Genetics, American Academy of Neurology, and American Academy of Pediatrics **recommend that all children with autism or autism-like features be referred to a clinical geneticist for a genetic evaluation**. These children may also benefit from seeing a developmental pediatrician.

What should I do if I suspect my patient has a rare disease?

1. Define the phenotype

When a rare disease is suspected, you as the PCP play a critical role in establishing a detailed history and phenotype, the collective combination of historical and physical features, together with laboratory and imaging findings, that characterize the patient's disease. **A well-defined phenotype can focus the diagnostic evaluation, potentially shortening the diagnostic odyssey.**

Phenotyping begins with an accurate, detailed history and physical examination that evaluates all body systems, reviews growth and diet, gauges development and behavior, and identifies possible dysmorphisms and other notable physical findings. The history should include a comprehensive family history and a review of any possible infectious, environmental, or occupational exposures that could account for symptoms.

This process may uncover a recognizable pattern or syndrome or may clarify which referrals and testing are most appropriate.

2. Refer to specialists

Your patient may need referrals to one or more specialists to refine the phenotype, perform specialized testing, and initiate a management plan. **Adequate and appropriate referrals can minimize diagnostic delays.** Sometimes choosing the best referral is straightforward, such as when signs and symptoms are mostly, if not entirely, related to one organ system. Other times, findings may not suggest one specific specialty and may require a multidisciplinary approach.

Finding a specialist familiar with rare diseases can be challenging, although many community specialists can and do diagnose rare diseases. However, if local referrals are not providing a diagnosis for your patient or a referral to medical genetics may be beneficial, consider referring to an academic medical center, particularly institutions designated as a NORD Rare Disease Centers of Excellence. Through the designation process, the NORD Rare Disease Centers of Excellence have demonstrated their capabilities and commitment to diagnosing, managing, and researching rare diseases.

3. Coordinate care

As the PCP, you are an invaluable source of continuity throughout the diagnostic odyssey. You gain a level of insight by providing:

Routine health supervision

Developmental surveillance

Recommended childhood immunizations

Management of acute illnesses

TAKE ACTION

Some presentations may benefit from expertise within a specialty, if access to such subspecialty care is available in a timely fashion.

For example:

- Children with **progressive weakness** should be evaluated by a **neuromuscular neurologist,** especially if electromyography is required.
- Children with **suspected metabolic disease** should receive biochemical testing and be evaluated by a **clinical geneticist specializing in biochemical disorders.**
- Children with **vision abnormalities and neurologic concerns** should be seen by a **neuro-ophthalmologist.**

These insights will enable you to inform specialist evaluations and maximize outcomes for children living with a rare disease. Many rare disease evaluation teams find comprehensive care summaries from PCPs helpful and will often maintain a dialogue with the PCP throughout an evaluation to gain additional context. Health Summary Templates developed by the Undiagnosed Rare Diseases Network International can help you communicate, organize, and present your patient's medical history in an efficient format.

In addition to providing this crucial foundation of care, you may also help facilitate and navigate the process of undergoing specialist evaluations.

As the PCP, you play an essential role in facilitating diagnostic access, the ability to be evaluated in a health care environment with the requisite knowledge, experience, and resources capable of producing a timely, accurate, and satisfactory explanation for their patient's signs and symptoms.

Sometimes this consists of placing a well-timed call to a trusted colleague and friend to gain additional perspective. Other times, this role takes the form of aggregating various assessments and recommendations from numerous specialists into a unified impression and plan before then engaging in shared decision-making with your patient and their family.

Wait times to see a specialist may sometimes be as long as two years. During the interim, you may be the main caretaker for the patient and may need to coordinate with a specialist to order specialized testing prior to an in-person visit.

Most patients with a rare disease will require a medical team including their PCP and appropriate specialists for diagnosis and management. **It is important for you to remain involved as the central coordinator of medical care.**

Testing for Rare Diseases

Some rare diseases have distinct physical, laboratory, or imaging findings that allow for diagnosis and management without genetic testing. Other times these assessments provide essential phenotypic information but are not always sufficient for diagnosis.

In most instances, testing for rare diseases involves some form of genetic testing and may sometimes include biochemical testing.

Genetic testing

While some rare diseases do not have a genetic basis, most do. The majority of patients with a rare or otherwise undiagnosed condition will have genetic testing at some point during their diagnostic odyssey. Specialized genetic testing is best ordered and interpreted by a clinical genetic specialist; however, if access to an in-person specialist evaluation is limited or otherwise delayed, it may be possible to collaborate remotely and order certain specialized genetic testing while awaiting an in-person evaluation.

Most genetic testing investigates whether there is a change in the structure, number of copies, or sequence in a gene or segment of genetic material. Phenotypic data are frequently used to assist in interpreting results, which report if a genetic variant, or change in the genetic code, has been detected and the significance of that variant. **Understanding variant classification is crucial to interpreting genetic testing results.**

Five types of genetic variants

Genetic variants are classified into one of five categories:

- Pathogenic
- Likely pathogenic
- Variant of uncertain significance (VUS)
- Likely benign
- Benign

Pathogenic or **likely pathogenic** variants are strongly associated with disease. A patient is often diagnosed with a genetic disorder if the pathogenic/likely pathogenic variant(s) result in disease, depending on the mode of inheritance for that gene and condition.

A variant is classified as a **variant of uncertain significance (VUS)** when its impact is unknown, because the specific variant has not been identified often enough or studied sufficiently to understand its effect, and predictive modeling cannot definitively determine its effect. **A patient should not be diagnosed or treated based on the presence of a VUS because there is insufficient evidence to know if that variant is contributing to their symptoms or not.**

Benign or **likely benign** variants are known or are strongly predicted not to cause any significant effect on the structure or function of the gene's protein product and are not associated with disease. Most genetic testing results do not include benign or likely benign variants, since we all have countless benign/likely benign variants.

Guidelines for testing from the American College of Medical Genetics and Genomics (ACMG) and other organizations clarify the overall processes for genetic testing, variant interpretation, and classification.

80%

of all rare diseases are genetic.

Boat, 2015, Wright et al., 2018.

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Types of genetic testing

Testing for copy number variants and other structural variants

Karyotyping and fluorescence in situ hybridization (FISH) analysis

Karyotyping evaluates the number and basic structure of chromosomes and is one of the only clinically available tests capable of identifying certain types of structural variants such as Robertsonian translocations and balanced translocations. Karyotyping is also critical in prenatal genetic diagnosis.

FISH uses specific probes to identify if certain larger segments of genes or chromosomes are missing or are present in an abnormal copy number. These assays are useful for identifying aneuploidy (e.g., Trisomy 21, Klinefelter syndrome, Turner syndrome), chromosomal rearrangements, and some deletion or duplication syndromes with large alterations such as Wolf-Hirschhorn syndrome.

Karyotyping and FISH results are typically reported as normal or abnormal and are often interpreted without regard to phenotype; as such, **an abnormal result does not necessarily mean that the structural change is disease-causing**. However, the resolution of karyotyping is limited, so deletions or duplications that are visible by chromosome analysis are often pathogenic. FISH has mostly been supplanted by microarray analysis.

Microarray analysis

Microarray analysis assesses for the presence of copy number variants (CNVs), such as microdeletions, microduplications, unbalanced translocations, or abnormal chromosome copy numbers. Assays based on the detection of single nucleotide polymorphisms can identify regions of homozygosity (ROH) that suggest consanguinity, uniparental disomy, or imprinting disorders. Microarrays cannot identify balanced genomic rearrangements. This test is typically ordered when chromosome duplication or deletion syndromes, such as DiGeorge, Cri du chat, Prader-Willi, or others are suspected. It is also often part of the workup for patients with multiple congenital anomalies, developmental delays, intellectual disabilities, and/or autism.

Microarray interpretation does not typically take the patient's phenotype into consideration when classifying variants and reporting results. Reports include any CNVs that are classified as pathogenic, likely pathogenic, or variant of uncertain significance (VUS). Results will also include regions of ROH. Pathogenic and likely pathogenic CNVs are strongly associated with disease or at least disease risk, while VUSs are of indeterminate significance. Regions of homozygosity are not necessarily indicative of pathogenicity, but rather indicate possible consanguinity, uniparental disomy, or an imprinting disorder and the associated risk of disease.

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Testing for sequence variants

Gene panels

Gene panels assess specific genes known to be associated with a phenotype, such as intellectual disability, autism, epilepsy, neuromuscular disorders, or cardiac abnormalities. The number of genes on a panel can vary from a small handful to several thousand. Gene panels often provide a higher level of sequencing coverage than broader exome or genome sequencing tests and include copy number variant (CNV) analysis.

However, advances in gene discovery can lead to rapid expansion in the list of genes associated with a phenotype, and panels can become quickly outdated. As such, nondiagnostic panel studies typically require further testing with broader exome or genome sequencing.

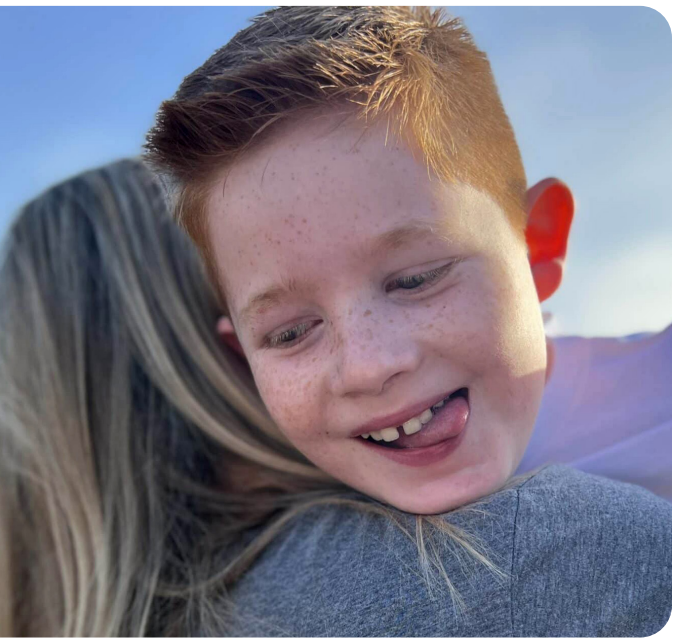
Furthermore, panel testing is typically only performed on the patient and thus cannot determine whether variants are on the same copy of the gene or are on different copies, or if the variants have been inherited from a parent or occurred de novo. Demonstrating inheritance patterns can assist in determining whether a variant is pathogenic (e.g., if a parent with the same variant has the same or similar symptoms as the patient, then the variant is more likely to be pathogenic), and as such, further testing may be required if determining inheritance patterns is needed.

Panel results are typically reported as positive, negative, or uncertain and include any pathogenic, likely pathogenic, or VUS variants found on the panel without regard to the patient's phenotype. Some variants have disparate phenotypes, and it is up to clinicians to decide if these variants are consistent with the patient's phenotype. Attributing pathogenicity also requires assessing the mode of inheritance. For example, if your patient has only one pathogenic variant for an autosomal recessive disorder, then they may only be a carrier of that disorder and may have no symptoms related to that variant.

Exome and genome sequencing

Exome and genome sequencing are the most comprehensive clinical genetic tests available and have the highest diagnostic yield of any single genetic test. Even so, diagnostic yields are typically less than 50%.

These tests are ideally performed on the patient with samples (and consent) from both biological parents. Including parental samples, when available, increases the diagnostic yield. Exome sequencing assesses approximately 95% of exons, the portions of genes that are expressed or translated into protein products, while genome sequencing assesses nearly 98% of all base pairs in the genome.



Genome sequencing usually includes CNV analysis, whereas exome sequencing typically does not to the same extent. Genome sequencing can also detect some structural rearrangements, such as balanced translocations.

While genome sequencing offers the advantage of sequencing nearly every base pair, our knowledge of disease-causing variants outside of exons and splice sites is still limited. Despite the comprehensive nature of both exome and genome sequencing, certain genes and segments of the genome cannot be evaluated by these modalities. Additionally, genome sequencing may not detect specific types of genetic variants such as Robertsonian translocations, trinucleotide repeat diseases, and abnormal methylation patterns; if such changes are suspected, specific testing is required.

Exome and genome sequencing reports often include multiple sections including a section for variants thought to be causing the patient's phenotype, a section for variants of uncertain clinical significance (VUS), and a section for secondary findings.

Exome and genome sequencing are interpreted using any provided phenotypic data; therefore, accurate and detailed phenotypic information are essential. A report that is positive for variants causal for the patient's phenotype typically only includes pathogenic/likely pathogenic variants of the appropriate zygosity and inheritance mode for the disease; as such, a physician can confidently diagnose and treat a patient based on the reported pathogenic/likely pathogenic variant.

Variants in the VUS section are not clinically actionable, but there is insufficient evidence to determine if they are benign or pathogenic. Reports that are not definitively diagnostic are dynamic; therefore, further testing of family members, periodic reanalysis, or advances in gene discovery may result in a VUS being reclassified as either pathogenic or benign.

Variants reported in the secondary findings section are pathogenic variants that cause disease but are not associated with the phenotype for which the patient is being tested. These are often later onset diseases for which treatments are available, such as cancer or cardiomyopathy. Pre-testing genetic counseling is used to determine how and if patients and families want secondary findings disclosed.

The clinical genetic specialists at our NORD® Rare Disease Centers of Excellence have the expertise and experience to interpret even the most complex genetic test results.

Biochemical testing

You may be familiar with certain biochemical tests but less familiar with specialized biochemical tests. Specialized biochemical tests are best ordered and interpreted by a clinical biochemical genetic specialist; however, if access to an in-person specialist evaluation is limited or otherwise delayed, it may be possible to collaborate remotely and order certain specialized metabolic testing while awaiting an in-person evaluation.

Inherited metabolic disorders (also referred to as inborn errors of metabolism) are diseases in which there is failure in the breakdown or storage of carbohydrates, proteins, or fats. Signs and symptoms include encephalopathy, hypoglycemia, acidosis, poor feeding, hypotonia, seizures, developmental delay, and intellectual disability.

Types of biochemical testing

- Neonatal screening panels
- Basic biochemical
- Specialized metabolic testing

Standard **neonatal screening panels,** i.e., newborn screening (NBS), completed on all newborns in the United States, may identify up to 50 different conditions including metabolic disorders, but the conditions on a panel vary state by state. Newborn Screening In Your State (HRSA) provides a list of conditions screened in each state and contact information for that state's NBS program. As a screening test, a normal result provides reassurance but does not eliminate the possibility of a metabolic disorder. If you suspect your patient may have a metabolic disorder or other rare disease, ensure that they had newborn screening performed and review the results.

Basic biochemical testing can identify changes in acid-base status, blood glucose levels, calcium homeostasis, ammonia metabolism, and other metabolic processes, as well as the presence of end-organ dysfunction, such as renal insufficiency or hepatic injury or dysfunction.

Specialized metabolic testing looks for the accumulation of abnormal metabolites; the patterns of abnormalities can suggest a category of metabolic disorders or be diagnostic of a specific disorder. In general, these tests are most valuable if collected when the patient is acutely symptomatic and under metabolic stress, such as when fasting or acutely ill.

Certain disorders, however, demonstrate characteristic baseline abnormalities even when the patient is asymptomatic. Some tests have strict collection and processing requirements and can return false positive or false negative results if improperly handled. Specialized metabolic testing often detects clinically insignificant abnormalities, so all results should be interpreted with caution and with the assistance of a specialist.

The most widely used tests for a suspected metabolic disorder are a complete metabolic panel, ammonia, lactate, pyruvate levels, plasma amino acids, urine organic acids, and plasma acylcarnitine profile. These tests detect many types of metabolic disorders, including aminoacidopathies, organic acidurias, urea cycle defects, and fatty acid oxidation defects. Other tests, such as creatine kinase levels or growth differentiation factor-15 (GDF-15) levels, can be helpful depending on presenting features.

Confirmation of a diagnosis may require enzyme activity assays or genetic testing. Some metabolic disorders cannot be detected by common biochemical tests and can only be diagnosed via genetic testing.

Examples of specialized metabolic testing

Comprehensive metabolic panel
A comprehensive metabolic panel (CMP) provides valuable information about blood glucose levels and acid-base status. Elevations in alanine transaminase (ALT) and aspartate transaminase (AST) are seen in certain metabolic diseases but may also be caused by a variety of nongenetic diseases. Some disorders may be associated with electrolyte abnormalities, renal insufficiency, or changes in calcium homeostasis.

Lactate
Lactate is a byproduct of normal metabolism and exercise but may be pathologically elevated in a variety of metabolic disorders that cause lactic acidosis. Specimen collection and processing errors may falsely elevate lactate levels.

Pyruvate
In the setting of elevated lactate levels, an elevated lactate-to-pyruvate ratio may indicate mitochondrial disease.

Macroscopic urinalysis
Urine pH, ketone levels, and glucose levels can help distinguish among various metabolic disorders. These determinations are most valuable when patients are acutely symptomatic. For example, the presence or absence of ketonuria in the setting of hypoglycemia can narrow the differential diagnosis of suspected metabolic disorders considerably.

Ammonia
Significantly elevated ammonia levels can be seen in metabolic disorders, including urea cycle defects and organic acidurias. When symptomatic, patients with these disorders are typically acutely ill and encephalopathic in correlation with the elevation in ammonia. Testing children who are at their neurologic baseline may lead to false positives, as specimen collection and processing errors can falsely elevate ammonia levels.

Plasma amino acids
A plasma amino acid test measures the levels of amino acids in the blood and can assist in the diagnosis of aminoacidopathies, urea cycle defects, and other disorders.

Urine organic acids
Measuring levels of organic acids excreted in the urine can help with the diagnosis of metabolic disorders such as organic acidurias or fatty acid oxidation defects.

Acylcarnitine profile
This test measures the amount of carnitine and its esters in the blood. Carnitine transfers fatty acids into the mitochondria for energy production and acylcarnitines help with the elimination of metabolic byproducts. Enzymatic defects may lead to the accumulation of abnormal acylated compounds; an acylcarnitine profile identifies these compounds and aids in the diagnosis of disorders of fatty acid oxidation, organic acidurias, and other metabolic diseases.

Growth differentiation factor-15 (GDF-15)
In patients with suspected metabolic disorders, an elevated GDF-15 level may indicate mitochondrial disease.

Creatine kinase (CK)
An enzyme present in many tissues, creatine kinase is found extensively in muscle. In patients with muscle weakness or myalgia, elevated CK levels may be evidence of a hereditary structural or metabolic myopathy, or of acquired muscle tissue injury.

What Should I Do if My Patient is Diagnosed With a Rare Disease?

Continue routine care and more

When a rare disease is diagnosed, the PCP remains an important part of the care team and often co-manages the patient with appropriate specialists. You will likely continue to manage common childhood conditions, coordinate specialists and therapists, and keep an eye on the bigger picture, making sure the patient and family receive the best support available.

Learn about the rare disease

Ascertain information about your patient's rare disease diagnosis from the reliable resources found in the Sources for Rare Disease Information section. Disease-specific patient advocacy organizations may also be excellent sources and provide additional insight from the parent perspective. However, information may be very limited, and most rare diseases do not have a patient advocacy group. In these cases, case reports or series in published medical and scientific journals may be all that is available at the time of diagnosis. Your patient and their caregiver are also invaluable sources of information.

Build a team

Collaborate with the diagnosing clinician to identify the types of specialists needed on your patient's care team. In some cases, care may be managed locally. In others, expertise found at a major academic medical center may be essential. In most cases, a hybrid of both approaches provides the best outcomes. If possible, assist your patient's parent/caregiver to identify a specialist or rare disease-specific multidisciplinary or specialized clinic for their child's rare disease or a complex care program at a NORD Rare Disease Center of Excellence or other academic medical center.

Manage expectations

Help your patient and their caregiver understand that due to their rarity, data or information regarding rare disease pathology, prognosis, and effective treatments may be lacking. Some rare diseases have

published evidence-based treatment guidelines or management resources, but many rely on symptom management. However, a diagnosis is invaluable to help connect with others, gain needed services, take advantage of medical and scientific advancements, and become involved in research.

Provide supportive resources

Connect families to supportive resources found in Resources to Connect Patients to Support to assist with overcoming challenges associated with a rare disease diagnosis.

Discuss enrolling in a clinical trial

Take the time to discuss clinical trial opportunities with your patients and their parents/caregivers and see if any are available that include pediatric patients with the child's rare disease. Clinical trials offer opportunities for testing, monitoring, and emerging therapeutics that might not otherwise be available. Further, participation in these clinical trials may help future patients to benefit from the information learned from them.

You can check NORD's Find Clinical Trials & Research Studies or the more comprehensive listing of clinical trials, ClinicalTrials.gov. Research studies and clinical trials are also listed on NORD Rare Disease Reports.

What To Do if My Patient Remains Undiagnosed?

Request reanalysis of genetic testing

Nondiagnostic genetic testing results do not necessarily exclude the possibility of genetic disease. Instead, results may indicate the limitations of our current clinical genetic testing technologies, our understanding of pathophysiology and the relationship between a specific gene and disease, or our ability to otherwise attribute pathogenicity to certain genetic changes. Patients with nondiagnostic genetic testing results may benefit from periodically having their genetic information reanalyzed, as new disease-associated variants are constantly being identified. They may also be candidates for research studies that employ testing modalities that are not commonly clinically available.

Manage expectations

The diagnostic success rate for genetic evaluation still approaches only 50%, and many patients will remain undiagnosed for prolonged periods of time despite everyone's best efforts. With rare diseases, answers can also be rare and effective treatments even rarer. Remaining engaged and committed to the diagnostic odyssey will allow for patients, parents/caregivers, and providers to take advantage of new diagnostic opportunities as they arise.

Be patient and remain involved

The diagnostic odyssey can be an immensely stressful process for patients and families, involving significant physical, emotional, and financial hardship. Knowing when to actively engage with further diagnostic efforts and when to temporarily pause is a shared decision-making process can be challenging. Periodically review your patient's management plans to assess polypharmacy, quality of life, and overall well-being.

Build a team

The diagnostic odyssey can similarly be challenging for medical providers and can contribute to burnout. A team-based approach to rare disease diagnosis and care can minimize these stressors, broaden the collective knowledge base, and suggest novel diagnostic approaches.

Consider additional clinical opinions

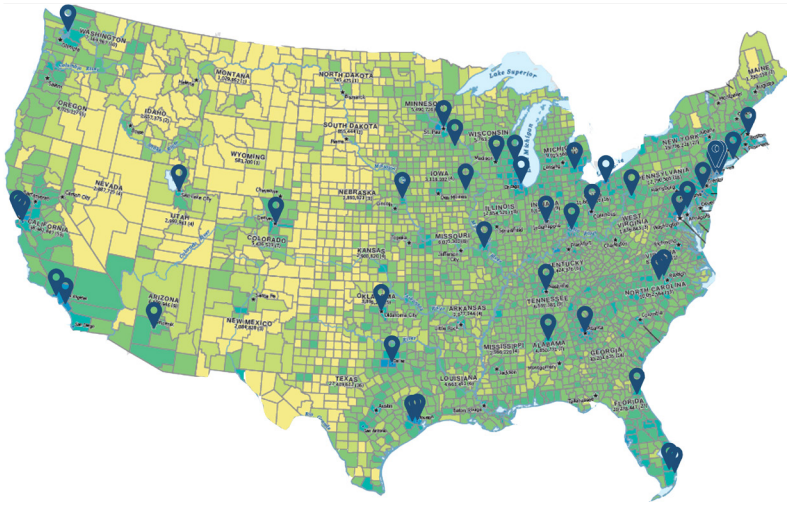
The NORD Rare Disease Centers of Excellence Program is the first national network of U.S. hospitals and academic medical institutions dedicated to diagnosing, treating, and researching all rare diseases. The 40 NORD Rare Disease Centers of Excellence are multi-institutional with broad specialist representation. Many have outreach clinics across their home states and/or provide care to rare disease patients in nearby states.

To learn more about the NORD Rare Disease Centers of Excellence Program, including how to refer your patient, please see Frequently Asked Questions about NORD Rare Disease Centers of Excellence *(en español: Sobre Los Centros de Excelencia)*.

Find a research-based undiagnosed program

When comprehensive clinical testing at an academic medical center has been exhausted, consider referring your patient to a research-based undiagnosed disease program for further evaluation. Many of the NORD Rare Disease Centers of Excellence have research-based undiagnosed disease programs that provide research diagnostic testing options not yet available in clinical settings.

Many of the undiagnosed programs at the NORD Rare Disease Centers of Excellence are independent institutional programs and referrals are made directly. Contact information for these programs can be found using the Directory for Rare Disease Centers of Excellence. Some of their undiagnosed programs are part of the Undiagnosed Diseases Network (UDN), a research consortium initially funded by the National Institutes of Health (NIH). UDN sites rely on a central application process. Academic medical centers outside of the NORD Rare Disease Centers of Excellence Program may also have a research-based undiagnosed disease program.



Rare Disease Information and Supportive Resources

Sources for rare disease information

NORD Rare Disease Database

Provides clinicians, patients, and families with information resources for over 10,000 rare diseases, including links to GeneReviews, Orphanet, Online Mendelian Inheritance in Man (OMIM), and MedlinePlus Genetics. In addition, the NORD Rare Disease Database contains more than 1,300 NORD Rare Disease Reports in English and over 500 in Spanish. NORD Rare Disease Reports:

- Tend to be more patient- and family-friendly than other resources but can also be a good place to start for clinicians and allied health professionals.
- Provide an overview of signs and symptoms, causes and inheritance, disorders with similar symptoms, diagnosis, standard therapies, and clinical trials and studies.
- Include a list of relevant patient advocacy, support groups, and other resources for patients.
- List references, and a growing number will include in-text citations.
- Are authored and/or reviewed by medical specialists.

NORD Rare Disease Video Library of CME Courses

Provides accessible, engaging digital courses to equip healthcare providers and patients with the information they need to identify the signs and symptoms of rare diseases and make sure they are familiar with available treatment options. The library includes four general introductory rare disease courses and a small but growing number of courses focused on specific rare diseases. The courses are developed by NORD and Medlive.

GeneReviews®

Provides clinicians with clinically relevant and medically actionable information for inherited conditions in a standardized journal-style format covering diagnosis, management, and genetic counseling for patients and their families.

Each chapter in GeneReviews is written by one or more experts on the specific condition or disease, and goes through a rigorous editing and peer review process before being published online. There are more than 800 chapters on specific genetic rare diseases. GeneReviews database is managed by the University of Washington.

MedlinePlus® Genetics

Provides clinicians, patients, and families with information on more than 1,300 health conditions with a genetic basis, more than 1,400 genes, and basic genetic concepts. The information is written in lay language and includes links to additional information and resources. MedlinePlus is a service of the National Library of Medicine (NLM), which is part of the National Institutes of Health (NIH).

Online Mendelian Inheritance in Man (OMIM®)

Provides referenced overviews on all known Mendelian disorders and more than 16,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain links to other genetics resources and relevant published articles. OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Ada Hamosh, MD, MPH.

Orphanet

Provides clinicians with high-quality information on more than 6,000 genetic and rare diseases with the aim of improving the diagnosis, care, and treatment of patients with rare diseases. Some resources are available in languages other than English. Orphanet is based in Europe and funded by the French National Institute for Health and Medical Research and the Health Programme of the European Union.

Resources to connect patients to support

NORD's Organizational Database

Offers a disease searchable listing of rare disease support and advocacy groups to help you connect your patient and their family to needed support. The support group may be dedicated to a single rare disease or a group of related or similar rare diseases. Many groups advance research for their rare disease(s). Disease-specific non-profit patient advocacy and support groups may:

- Provide information about their rare disease(s), including diagnosis and management, in family-friendly language.
- Connect families with others living with the same rare disease or facing similar challenges.
- Offer or link to supportive services and assistance programs.
- Share information about rare disease research and clinical study opportunities.
- Include a list of specialists or expert centers for diagnosis or care.

The scientific and medical advisory boards or board of directors of a patient group may also help identify specialists in the disease. These groups can facilitate a clinician-to-clinician connection if the specialist's contact information is not included on their website. Some patient groups also provide clinicians with information developed by specialists of the disease.

NORD State Resource Center

Contains state-specific organizations that offer free or low-cost programs and services for individuals impacted by rare disease.

Please call NORD at **1-844-259-7178** or email us at **informationservices@rarediseases.org**.

Si deseas hablar con alguien en espanol por favor llame al ***(844) 259-7178*** *para asistencia.*

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NORD Support Helpline

Helps patients and families navigate a variety of rare disease issues. Patients and families can contact NORD's dedicated Information and Resource Services team by phone or email. NORD has an assistance line for Spanish-speaking patients and families.

NORD RareCare® Patient Assistance Programs

Offers help to patients and families who need assistance paying for medical bills, traveling to a treatment center, or participating in clinical trials. NORD also offers support for parents/caregivers through our Caregiver Respite Program and helps cover costs associated with educational programs and conferences.

- Search NORD RareCare Patient Assistance Programs Database: Many of the programs are disease-specific, but new programs are added as funding becomes available.
- Applying for NORD Caregiver Respite: Provides financial assistance to enable parents/caregivers a break to attend a conference or to simply have time away from caregiving.
- Apply for NORD RareCare Rare Disease Educational Support Program: Designed to offer rare disease patients, their families, and/or parents/caregivers an opportunity to participate in educational programs and conferences that offer rare disease content.

Members of NORD's Patient and Information Services team

Selected Published Medical Articles

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Alone we are rare. Together we are strong.®

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