NORD®
National Organization for Rare Disorders

RareDx for Pediatricians:
A Primer to Diagnosing Rare Disease in Children



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

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I. Introduction

RareDx for Pediatricians provides information to support the recognition and evaluation of rare diseases in children. It is intended for pediatricians, family medicine clinicians, nurse practitioners, and other primary care professionals (PCPs) who care for children with unexplained symptoms, complex presentations, or conditions that do not follow typical patterns.

The content is designed to support PCPs by outlining practical considerations for evaluation, referral, and care coordination across the diagnostic process. Guidance is also included for situations in which a diagnosis is made, as well as for cases in which a diagnosis remains uncertain.

This primer does not replace clinical judgment or specialist consultation. If you have concerns about a child's health or development, continue to evaluate and manage the child according to established clinical standards and refer to appropriate specialists when indicated.

RareDx for Pediatricians was developed by a multidisciplinary working group of clinicians, researchers, genetic counselors, and laboratory experts affiliated with NORD® Rare Disease Centers of Excellence Network. This Network includes top academic and research institutions across the United States. NORD (the National Organization for Rare Disorders) is a U.S.-based rare disease nonprofit organization founded over 40 years ago by parents, patients, and clinicians to advocate for the well-being of people living with rare diseases and to advance diagnosis, care, and research.

A companion guide, *RareDx for Parents*, is available to support families as they partner with their child's primary care professional.



II. Understanding Rare Diseases & the Diagnostic Process

In the United States, a rare disease is defined as a condition affecting fewer than 200,000 people. Although individually, rare diseases are uncommon, collectively, they affect nearly 1 in 10 individuals. Most rare diseases have a known or suspected genetic basis, and many present during childhood.

Children with rare diseases often experience a prolonged and complex path to diagnosis. This process, commonly referred to as a diagnostic odyssey, typically begins in the primary care setting when a child presents with unexplained, atypical, or evolving symptoms. Evaluation may involve multiple specialists and repeated testing, and a diagnosis may take months or years, or may remain elusive. While not all rare diseases can currently be diagnosed, advances in medicine and genetics continue to expand diagnostic possibilities.

Primary care professionals play a central role throughout this process. You are often the first to recognize when a child's presentation does not fit common patterns, the primary source of continuity as evaluations unfold, and a trusted partner for families navigating uncertainty. Diagnostic delays are common in rare disease and often reflect limitations in current knowledge, evolving phenotypes, and the need to appropriately evaluate and exclude more common conditions.

The NORD Rare Disease Centers of Excellence Network was established to support earlier and more accurate diagnosis, coordinated care, and research across a broad range of rare diseases, while partnering closely with community-based clinicians.

> **!** PCPs play a critical role in recognizing the possibility of rare disease and guiding families through next steps.



Signs and symptoms: Recognizing the possibility of a rare disease

PCPs play a central role in recognizing the possibility of a rare disease, as you are often the first clinician to evaluate a patient when symptoms emerge. In some cases, a patient's presentation may not align with common conditions you encounter in routine practice, making early recognition challenging. Caregiver observations are often critical in this early phase and may provide important clues to atypical, subtle, or evolving disease that complement clinical findings.

Occasionally, pathognomonic findings or a clear family history point directly to a diagnosis. More often, however, rare diseases present with subtle, slowly progressive, multisystem, or atypical features that may resemble more common disorders.

In some situations, no single feature clearly suggests a rare disease. Instead, concern may arise from an overall clinical impression. If careful evaluation indicates that a patient's presentation is unlikely to represent an atypical form of a common condition, the combined effects of multiple common disorders, or adverse effects of medications, therapies, or environmental or infectious exposures, a rare disease should be considered.

As a general guide, when you and one or more appropriate specialists are unable to establish a diagnosis after multiple evaluations, the possibility of an underlying rare disease increases, and further targeted evaluation may be warranted.

Findings that may indicate a rare disease include:


Functional or anatomic concerns identified on fetal ultrasound


Congenital anomalies


Medical problems involving more than one organ system or body part


Abnormal newborn screening results


Atypical growth patterns, including failure to thrive, accelerated growth, or disproportionate growth


Developmental delays or loss of previously acquired skills


Social or behavioral differences, including autism spectrum features


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


Symptoms that begin early in life or show progressive worsening


Illnesses that are unusually frequent, severe, prolonged, or resistant to standard treatment


A family history of similar, unexplained symptoms


Recurrent episodes of hypoglycemia or metabolic acidosis without a clear cause


Recurrent episodes of encephalopathy or ataxia

Critical role of the PCP

PCPs are essential to the early recognition and evaluation of rare diseases in children. Your role often includes:

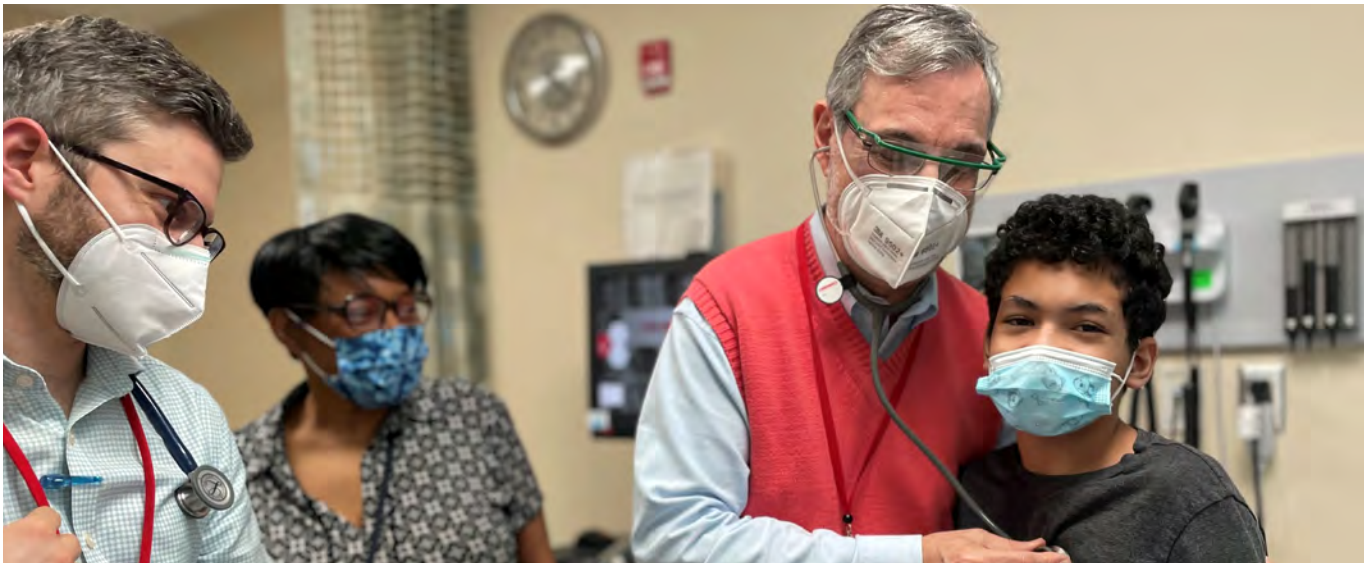
- Establishing a thorough medical history and phenotype
- Initiating specialist referrals to specialists and subspecialists
- Coordinating ongoing, multidisciplinary care

As the clinician most consistently involved in a child's care, you provide continuity throughout the diagnostic process. This continuity supports timely testing and evaluation, helps integrate information from multiple specialists, and allows changes in symptoms or function to be recognized over time. Early and sustained PCP involvement can shorten diagnostic delays and ensure children receive appropriate care as soon as concerns arise.

Clinical Consideration

Certain presentations warrant early referral and testing. Consider referral to a clinical geneticist for children with seizures and brain malformations, unexplained growth differences, or developmental delays.

Since 2025, the American Academy of Pediatrics (AAP) recommends exome or genome sequencing a first-tier diagnostic test for children with global developmental delay (GDD) or intellectual disability (ID). Professional organizations including the American College of Medical Genetics and Genomics (ACMG), American Academy of Neurology (AAN), and AAP also recommend genetic evaluation for all children with autism or autism-like features, with referral to developmental pediatrics or other specialists as indicated.



Next steps when a rare disease is suspected

1. Define the phenotype

When a rare disease is suspected, the PCP plays a central role in defining the patient's phenotype, i.e., the constellation of historical features, physical findings, and laboratory or imaging abnormalities that characterize the condition. A clearly defined phenotype can focus the diagnostic evaluation, guide referrals, and help shorten the time to diagnosis.

Phenotyping begins with a detailed medical history and comprehensive physical examination. This assessment should review all organ systems, growth patterns, diet, development, and behavior, and identify dysmorphic features or other notable findings. A thorough family history is essential, as is consideration of potential infectious, environmental, or occupational exposures that could contribute to symptoms.

This process may reveal a recognizable pattern or syndrome or help determine the most appropriate diagnostic testing and specialist referrals.

2. Refer to specialists

Many patients will require referral to one or more specialists to refine the phenotype, pursue specialized testing, and initiate management. Thoughtful and timely referrals can reduce diagnostic delays. In some cases, referral is straightforward, for example, when findings are confined to a single organ system. In other cases, multisystem or nonspecific findings may necessitate a multidisciplinary approach.

While many community-based specialists diagnose and manage rare diseases, referral to an academic medical center may be helpful when local evaluations are nondiagnostic or when expertise in medical genetics is needed. Institutions designated as NORD Rare Disease Centers of Excellence have demonstrated experience and commitment in diagnosing, managing, and researching rare diseases and may offer coordinated, multidisciplinary evaluation.

Subspecialty Referrals

When subspecialty expertise is available, early referral can help clarify diagnosis and guide testing.

Consider subspecialty referral when:

- Progressive muscle weakness is present → refer to a neuromuscular neurologist, particularly if electromyography is indicated.
- A metabolic disorder is suspected → initiate basic biochemical testing and refer to a clinical geneticist specializing in biochemical disorders.
- Vision abnormalities with neurologic findings are identified → refer to a neuro-ophthalmologist.

Timely, targeted referrals can reduce diagnostic delays and support coordinated care.

3. Coordinate care

Throughout the diagnostic process, the PCP provides essential continuity. Ongoing care typically includes:

- **Routine health supervision**
- **Developmental surveillance**
- **Recommended immunizations**
- **Management of acute illnesses**

This longitudinal perspective allows the PCP to contextualize evolving symptoms and inform specialist evaluations. 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.

PCPs also play a key role in facilitating access to specialty care, coordinating referrals, ordering recommended testing while awaiting appointments, and synthesizing input from multiple consultants. In some cases, this involves informal consultation with trusted colleagues; in others, it requires integrating disparate recommendations into a cohesive plan and engaging families in shared decision-making.

Given that specialty wait times may extend months or longer, the PCP often remains the primary clinician during this period. Most children with rare diseases ultimately require a care team that includes both the PCP and appropriate specialists, with the PCP serving as the central coordinator of care.



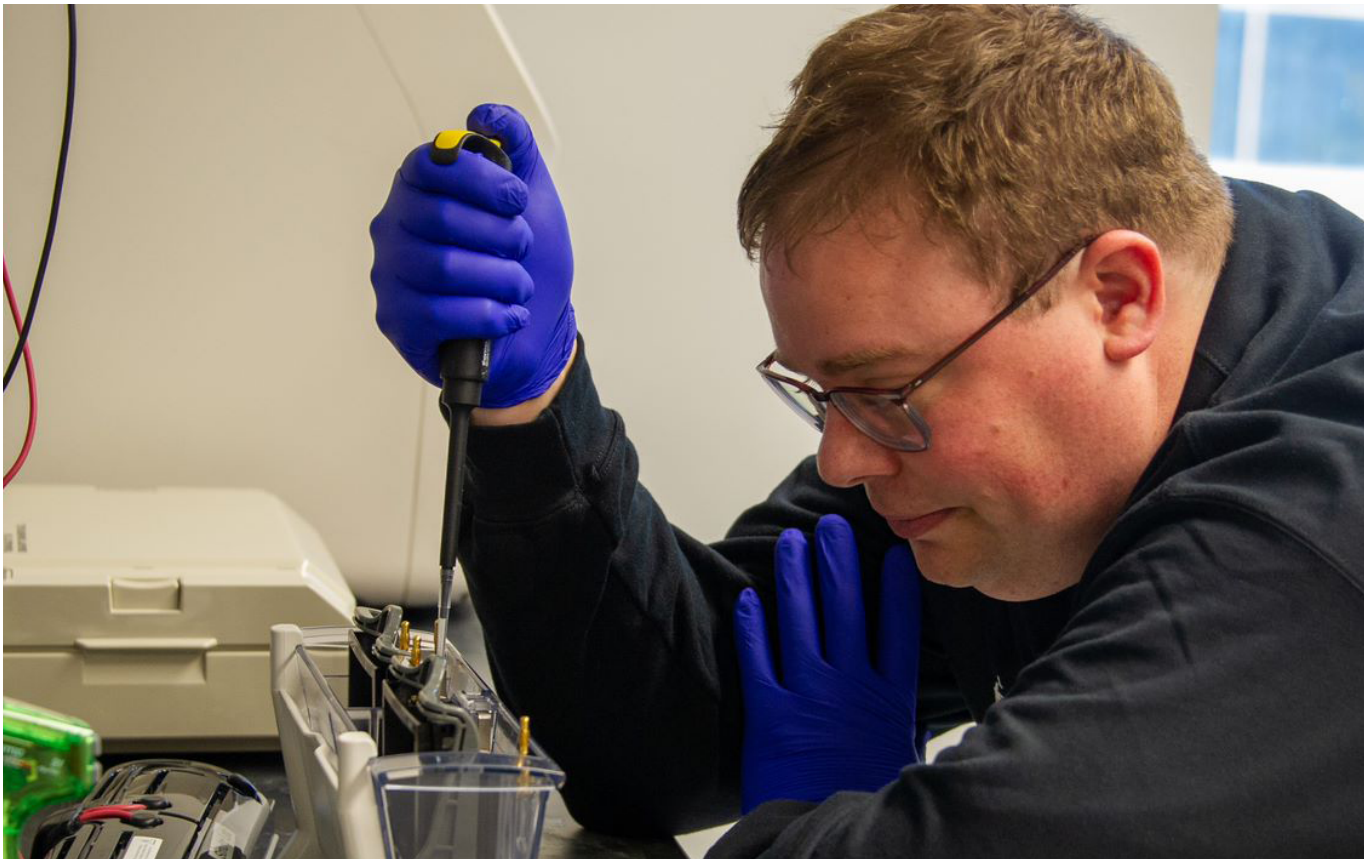
III. Testing for Rare Diseases

While some rare diseases can be diagnosed based on distinct physical features, characteristic laboratory findings, or specific imaging results, not all cases are so clear-cut. In many situations, these assessments provide valuable phenotypic information that helps narrow the differential diagnosis but may not be sufficient to confirm a rare disease on their own.

Not all tests are appropriate for every patient; test selection should be guided by the patient's phenotype, pretest probability, and input from relevant specialists. A targeted, stepwise approach can help avoid unnecessary testing while maximizing diagnostic yield.

In most cases, genetic testing plays a central role in the diagnostic process. In certain scenarios, particularly when a metabolic or enzyme deficiency is suspected, biochemical testing may also be essential, either as a first-line approach or to complement genetic results.

Determining when and how to pursue these tests and interpreting them in the context of a patient's phenotype, often requires coordination with clinical genetics or other specialists experienced in rare disease evaluation.



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

Interpreting genetic test results is a key step in the diagnostic process for patients with suspected rare diseases. Variants identified through genetic testing are categorized based on the strength of available evidence regarding their association with disease.

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 and may be considered causative of the patient's symptoms, depending on the gene involved and the mode of inheritance. For autosomal recessive conditions, two disease-causing variants, one on each copy of the gene (biallelic variants), are typically required for a diagnosis. In contrast, a single variant may be sufficient for autosomal dominant or X-linked disorders, depending on the specific context.

When a **pathogenic or likely pathogenic variant** is consistent with the clinical phenotype and inheritance pattern, a genetic diagnosis can often be made, guiding both management and family risk assessment.

A **variant of uncertain significance (VUS)** is a genetic change for which there is insufficient or conflicting evidence about its role in disease. A VUS may be rare or novel, and current data, such as case reports, functional studies, or population frequency, may be lacking or inconclusive. As a result, the clinical significance of the variant remains unclear.

A VUS should not be used as the sole basis for diagnosis or medical decision-making. Management should not be altered solely based on a VUS, and patients should not be labeled with a genetic condition unless and until reclassification occurs. In some cases, additional testing (e.g., family studies, biochemical testing, functional assays) may help clarify a VUS over time.

Benign or likely benign variants are not associated with disease. These are often common changes in the general population or are predicted not to affect protein function. Genetic testing reports usually do not list benign or likely benign variants unless they are relevant to the differential diagnosis, as each person carries numerous such 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. These guidelines help laboratories classify variants and provide a framework for clinicians to apply results appropriately in patient care.

Types of genetic testing

Karyotyping and fluorescence in situ hybridization (FISH)

Karyotyping evaluates the number and overall structure of chromosomes and remains one of the few clinically available tests capable of identifying certain structural rearrangements, such as balanced translocations and Robertsonian translocations. It continues to play an important role in prenatal diagnosis and may also be used in the evaluation of infertility and recurrent pregnancy loss.

Fluorescence in situ hybridization (FISH) uses targeted probes to assess whether specific chromosomal regions are missing or present in abnormal copy numbers. FISH can detect aneuploidy (e.g., trisomy 21, Turner syndrome, Klinefelter syndrome), chromosomal rearrangements, and select large deletion or duplication syndromes, such as Wolf–Hirschhorn syndrome.

Results from karyotyping and FISH are typically reported as normal or abnormal and are often interpreted without direct consideration of thepatient's phenotype. As a result, not all identified chromosomal changes are clinically pathogenic.For example, a balanced translocation may not cause symptoms but can have important reproductive implications. In contrast, large deletions or duplications detectable by standard karyotyping are more likely to be clinically significant.

In current practice, FISH has largely been supplanted by chromosomal microarray analysis, which offers higher resolution for detecting copy number changes.

Microarray analysis

Chromosomal microarray analysis evaluates the genome for copy number variants (CNVs), including microdeletions, microduplications, unbalanced translocations, and abnormal chromosome copy numbers. SNP-based microarrays can also detect regions of homozygosity (ROH), which may suggest consanguinity, uniparental disomy, or certain imprinting disorders. Microarray analysis cannot detect balanced chromosomal rearrangements.

Microarray testing is commonly ordered when chromosome deletion or duplication syndromes (e.g., DiGeorge syndrome, Cri-du-chat syndrome, Prader-Willi syndrome) are suspected. It is also frequently included in the evaluation of patients with multiple congenital anomalies, developmental delay, intellectual disability, and/or autism.

Microarray results are reported independently of the patient's clinical presentation and include CNVs classified as pathogenic, likely pathogenic, or variants of uncertain significance (VUS), as well as any identified ROH. Pathogenic and likely pathogenic CNVs are strongly associated with disease or increased disease risk. VUS findings have unclear clinical significance and should not be used in isolation to establish a diagnosis. Regions of homozygosity do not indicate pathogenicity on their own but may raise concern for consanguinity, uniparental disomy, or imprinting disorders and the associated risk of disease.

Interpretation of microarray findings should be guided by clinical context and, when needed, in collaboration with a genetics specialist.

Gene panels

Gene panel testing evaluates a defined set of genes known to be associated with a specific clinical phenotype, such as intellectual disability, autism, epilepsy, neuromuscular disorders, or inherited cardiac conditions. Panels can range from a small number of genes to several thousand. Compared with broader tests, gene panels often provide deeper sequencing coverage of the included genes and typically incorporate copy number variant (CNV) analysis.

Because gene discovery is rapidly evolving, panels can become outdated over time, either by missing newly identified disease-associated genes or by including genes later found not to be causative. As a result, nondiagnostic panel testing frequently necessitates follow-up testing with exome or genome sequencing.

Panel testing is usually performed on the affected patient alone and therefore cannot determine if multiple variants are located on the same copy of a gene (in cis) or on opposite copies (in trans), nor whether a variant was inherited or occurred de novo. Determining inheritance patterns can be critical for variant interpretation; for example, a variant shared by an affected parent and child is more likely to be pathogenic. Additional testing of family members may therefore be required.

Results are typically reported as positive, negative, or uncertain and include pathogenic, likely pathogenic, and variants of uncertain significance (VUS), regardless of clinical relevance. Clinical correlation remains essential, as some variants are associated with a broad or variable phenotype. Mode of inheritance must also be considered; for example, identification of a single pathogenic variant in an autosomal recessive condition usually indicates carrier status and is not expected to cause disease.

Exome and genome sequencing

Exome and genome sequencing are the most comprehensive clinical genetic tests currently available and offer the highest diagnostic yield of any single genetic test. Even so, diagnostic yields typically remain below 50%.

These tests are ideally performed as trio testing, which includes the patient and both biological parents (with appropriate consent). Parental samples significantly improve diagnostic yield and aid in variant interpretation. Exome sequencing evaluates approximately 95% of exons, the protein-coding regions of genes, whereas genome sequencing assesses nearly 98% of all base pairs in the genome.

Genome sequencing generally includes copy number variant (CNV) analysis and may detect certain structural rearrangements, such as balanced translocations, to a greater extent than exome sequencing. However, despite its breadth, our understanding of disease-causing variation outside of exons and canonical splice sites remains limited. In addition, some genomic regions and variant types are not reliably detected by either method. For example, genome sequencing may not identify Robertsonian translocations, trinucleotide repeat expansions, or abnormal methylation patterns, and targeted testing is required when these are suspected.

Reports from exome and genome sequencing typically include several sections: variants thought to explain the patient's phenotype, variants of uncertain significance (VUS), and secondary findings. Interpretation relies heavily on the quality and completeness of phenotypic information provided at the time of testing.

When a report identifies pathogenic or likely pathogenic variants consistent with the patient's phenotype and inheritance pattern, a molecular diagnosis can usually be established and used to guide care. Variants listed as uncertain are not clinically actionable and should not direct management. Nondiagnostic results are not static; periodic reanalysis, additional family testing, or advances in gene discovery may lead to future reclassification of variants.

Secondary findings include pathogenic variants unrelated to the indication for testing, often associated with later-onset, medically actionable conditions such as hereditary cancer syndromes or cardiomyopathy. Pre-test genetic counseling is essential to determine whether patients and families wish to receive these results.

Biochemical testing

PCPs are generally familiar with standard biochemical testing but may be less familiar with specialized metabolic testing. These tests are best ordered and interpreted in collaboration with a clinical biochemical geneticist. When timely in-person consultation is not available, remote collaboration with a specialist may allow appropriate testing to proceed while awaiting formal evaluation.

Inherited metabolic disorders, also known as inborn errors of metabolism, result from impaired breakdown or storage of carbohydrates, proteins, or fats. Clinical presentations are variable and may include encephalopathy, hypoglycemia, metabolic acidosis, feeding difficulties, hypotonia, seizures, developmental delay, or intellectual disability. Some disorders present acutely, while others follow a more indolent course.

Biochemical testing relevant to rare disease evaluation generally falls into three categories:

- Newborn screening (NBS)
- Basic biochemical testing
- Specialized metabolic testing

Standard newborn screening panels are performed for all infants in the United States and can identify up to 50 conditions, including select metabolic disorders. The conditions screened vary 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 tool, normal results are reassuring but do not exclude the possibility of a metabolic disorder. If metabolic disease is suspected, confirm that NBS was completed and review results carefully.

Basic biochemical testing evaluates core metabolic processes and organ function, including acid–base balance, glucose regulation, calcium homeostasis, ammonia metabolism, and renal or hepatic function.

Specialized metabolic testing assesses for abnormal accumulation of metabolites.

Specific biochemical patterns may suggest a category of metabolic disease or, in some cases, be diagnostic. These tests are often most informative when obtained during acute illness or metabolic stress, though some disorders demonstrate characteristic baseline abnormalities even when patients are asymptomatic.

Specialized testing requires careful specimen collection and handling, as improper processing can lead to false-positive or false-negative results. Incidental or clinically insignificant abnormalities are common; interpretation should therefore occur with specialist input.

Common first-line tests when a metabolic disorder is suspected include a comprehensive metabolic panel, ammonia, lactate, pyruvate, plasma amino acids, urine organic acids, and plasma acylcarnitine profile. Additional studies, such as creatine kinase or growth differentiation factor-15 (GDF-15), may be helpful based on clinical presentation.

Definitive diagnosis often requires enzyme activity assays or genetic testing. Some metabolic disorders cannot be identified through biochemical testing alone and require genetic testing confirmation.



Examples of specialized metabolic testing

The following laboratory studies are commonly used in the evaluation of suspected inherited metabolic disorders. Selection and interpretation should be guided by clinical presentation and, when possible, performed in consultation with a metabolic specialist.

Comprehensive Metabolic Panel (CMP)

A comprehensive metabolic panel (CMP) provides information on blood glucose, electrolyte balance, renal and hepatic function, and acid–base status. Elevations in alanine transaminase (ALT) and aspartate transaminase (AST) may be seen in some metabolic disorders but are nonspecific and can result from many non-genetic conditions. Certain metabolic diseases may also present with electrolyte abnormalities, renal dysfunction, or altered calcium homeostasis.

Lactate

Lactate is a normal byproduct of metabolism and exercise but may be pathologically elevated in disorders associated with lactic acidosis, including mitochondrial disease. Improper specimen collection or delayed processing can falsely elevate results.

Pyruvate

When lactate is elevated, the lactate-to-pyruvate ratio may help distinguish between disorders of mitochondrial energy metabolism and other causes of lactic acidosis.

Macroscopic Urinalysis

Urine pH, ketones, and glucose can help differentiate among metabolic disorders, particularly during acute illness. For example, the presence or absence of ketonuria in the setting of hypoglycemia can significantly narrow the differential diagnosis.

Ammonia

Marked hyperammonemia may be seen in urea cycle defects and organic acidurias and is often associated with acute encephalopathy. Ammonia levels are highly sensitive to collection and handling; testing patients at neurologic baseline may yield false-positive results.

Plasma Amino Acids

Quantitative plasma amino acid analysis assists in the diagnosis of organic acidurias, urea cycle disorders, and related conditions.

Urine Organic Acids

Measurement of organic acids excreted in urine can identify patterns suggestive of organic acidurias, fatty acid oxidation disorders, and other metabolic diseases.

Acylcarnitine Profile

This test evaluates carnitine and its esterified forms. Abnormal acylcarnitine patterns may indicate defects in fatty acid oxidation, organic acid metabolism, or related pathways.

Growth Differentiation Factor-15 (GDF-15)

Elevated GDF-15 levels may support a diagnosis of mitochondrial disease in the appropriate clinical context.

Creatine Kinase (CK)

CK is abundant in muscle tissue. Elevated levels in patients with weakness or myalgia may suggest a hereditary metabolic or structural myopathy, though elevations are not specific and may reflect acquired muscle injury.

IV. Caring for Your Patient After a Rare Disease Diagnosis

Continue routine care and co-management

Following a rare disease diagnosis, the PCP remains a central member of the care team. You will continue to manage routine childhood health needs, monitor growth and development, address intercurrent illnesses, and help coordinate care across specialists and therapists. Your longitudinal relationship with the patient and family provides critical continuity and helps ensure that care remains comprehensive and patient-centered.

Learn about the rare disease

Use reliable sources, including those listed in the Resource Guide: Finding Reliable Information section, to familiarize yourself with your patient's rare disease. Disease-specific patient advocacy organizations can offer valuable clinical and family-centered perspectives when available, though many rare diseases lack formal advocacy groups. In some cases, medical literature, such as case reports or small case series, may be the primary source of information. Patients and caregivers themselves are also important partners and sources of insight.

Build and coordinate the care team

Work with the diagnosing clinician to identify the specialists needed to manage the patient's condition. Some care can be delivered locally, while other aspects may require expertise available at an academic medical center. A hybrid approach often provides the best balance. When possible, assist families in identifying multidisciplinary clinics, disease-specific programs, or complex care services, including those available through NORD Rare Disease Centers of Excellence.

Set realistic expectations

Help families understand that, because of their rarity, many conditions lack robust data on prognosis or evidence-based treatment guidelines. Management often focuses on symptom control and supportive care. Even so, a diagnosis can be transformative, facilitating access to services, educational supports, community connections, and emerging research opportunities.

Connect families to supportive resources

Link patients and caregivers to support services and educational resources, including those listed in Resource Guide: Connecting Patients to Support section, to help address the medical, emotional, and practical challenges associated with a rare disease diagnosis.

Discuss research and clinical trial opportunities

When appropriate, review available research studies or clinical trials that include pediatric patients with the diagnosed condition. Clinical trials may offer access to specialized evaluations or emerging therapies and contribute to broader understanding of rare diseases. Resources include 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 in NORD Rare Disease Reports.

V. Moving Forward Without a Diagnosis

Understand nondiagnostic genetic testing results

Nondiagnostic genetic testing does not exclude a genetic etiology. Instead, it may reflect current limitations in testing technologies, incomplete understanding of gene–disease relationships, or insufficient evidence to classify a detected variant as pathogenic. Patients with nondiagnostic results may benefit from periodic reanalysis of existing genetic data as knowledge and variant interpretation evolve. Periodic reanalysis should be viewed as part of longitudinal care rather than a separate diagnostic event. Some patients may also be candidates for research-based testing approaches not routinely available in clinical practice.

Set realistic expectations

Despite advances in genomic medicine, the overall diagnostic yield for genetic evaluation remains approximately 50%. Many patients will remain undiagnosed for extended periods despite thorough evaluation. In rare disease care, answers and effective treatments may be limited. Ongoing engagement in the diagnostic process allows patients, families, and medical professionals to take advantage of emerging diagnostic tools and discoveries as they become available.

Remain involved and support longitudinal care

The diagnostic process can be physically, emotionally, and financially taxing for patients and families. Determining when to pursue additional testing and when to pause further evaluation requires shared decision-making. Periodic reassessment of management plans is important to address polypharmacy, symptom burden, quality of life, and psychosocial needs while diagnostic efforts continue.

Use a team-based approach

Undiagnosed cases can also be challenging for clinicians and may contribute to professional fatigue. A multidisciplinary, team-based approach can distribute the burden of care, broaden diagnostic perspectives, and generate new hypotheses for evaluation. Collaboration across specialties helps sustain momentum and supports both patients and clinicians.

Seek additional clinical expertise

The NORD Rare Disease Centers of Excellence Network is a national network of U.S. hospitals and academic medical centers dedicated to diagnosing, treating, and researching rare diseases. The designated Rare Disease Centers of Excellence offer broad subspecialty expertise, multidisciplinary care models, and, in many cases, outreach clinics serving surrounding regions. Information on referral pathways is available through the Frequently Asked Questions about NORD Rare Disease Centers of Excellence. (En Español: Sobre Los Centros de Excelencia).

Consider research-based undiagnosed disease programs

When comprehensive clinical evaluation at an academic medical center has been exhausted, referral to a research-based undiagnosed disease program may be appropriate. Many NORD Rare Disease Centers of Excellence host such programs, offering access to advanced research diagnostics not yet available clinically. Some programs participate in the NIH-funded Undiagnosed Diseases Network (UDN), which uses a centralized application process, while others accept direct institutional referrals. Additional programs may also exist outside the NORD Network.

VI. Resource Guide: Finding Reliable 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

Offers accessible, engaging digital courses designed to enhance both clinician and patient understanding of rare diseases. Developed in partnership with Medlive, the library equips healthcare professionals with the tools to recognize key signs and symptoms, navigate the diagnostic process, and understand available treatment options. The collection includes four broad, introductory courses on rare diseases as well as a growing selection of disease-specific modules. These resources are intended to support continuing medical education (CME) while also fostering earlier recognition and improved care for individuals living with rare conditions.

NORD Video Library

The Rare Disease Video Library offers short educational videos in English and Spanish about rare diseases and related topics. These videos are made for patients, caregivers, doctors, students, and the general public. You can find videos that explain aspects of rare disease diagnosis, patient registries, research, clinical trials and genetic testing. The videos are available on NORD's YouTube channel.

GeneReviews®

An expert-authored, peer-reviewed resource that provides clinicians with clinically relevant, actionable information on inherited conditions. Each chapter follows a standardized, journal-style format and covers diagnosis, management, and genetic counseling considerations for patients and their families. Written by specialists in the relevant field and rigorously edited and reviewed before publication, the database currently contains more than 800 chapters on specific genetic rare diseases. Managed by the University of Washington, GeneReviews® serves as a trusted, comprehensive reference for evidence-based rare disease care.

MedlinePlus® Genetics

Offers accessible, evidence-based information on more than 1,300 genetic health conditions, over 1,400 genes, and key genetic concepts. Written in lay language, it is designed for use by clinicians, patients, and families, with links to additional trusted resources for deeper exploration. This service, provided by the National Library of Medicine (NLM) at the National Institutes of Health (NIH), helps bridge the gap between complex genetic science and patient understanding, supporting informed decision-making in rare disease care.

Online Mendelian Inheritance in Man (OMIM®)

Offers comprehensive, referenced overviews for all known Mendelian disorders and more than 16,000 genes, with a focus on the relationship between genotype and phenotype. Updated daily, each entry includes links to relevant literature, other genetics databases, and additional resources. While intended primarily for physicians, genetic professionals, and researchers, OMIM can also be valuable for advanced students in medicine and science. Authored and edited at the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins University School of Medicine, under the direction of Ada Hamosh, MD, MPH, OMIM remains an essential tool for understanding the genetic basis of rare diseases.

Orphanet

Provides clinicians with high-quality, peer-reviewed information on more than 6,000 genetic and rare diseases, with the goal of improving diagnosis, care, and treatment for patients with rare conditions. Resources include disease summaries, expert center directories, diagnostic tools, and information on clinical trials and research projects. Many materials are available in multiple languages, making Orphanet a valuable global resource. Based in Europe, Orphanet is funded by the French National Institute for Health and Medical Research and the Health Programme of the European Union.



VII. Resource Guide: Connecting 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, financial assistance programs, and educational resources.
- Share updates on research and clinical trial opportunities.
- Maintain lists of specialists or expert centers for diagnosis and care.

Some groups' medical or scientific advisory boards may also assist in identifying disease experts and can facilitate clinician-to-clinician connections. Many organizations provide materials developed by specialists, ensuring both patients and clinicians have access to reliable, up-to-date information.

NORD State Resource Center

Provides a searchable directory of state-specific organizations that offer free or low-cost programs and services for people affected by rare diseases. These resources can include access to financial assistance, transportation support, advocacy services, and other community-based programs. By connecting patients and families with local support, the State Resource Center helps bridge gaps in care, address non-medical needs, and improve overall quality of life.

NORD Support Helpline

Connects patients and families with NORD's Information and Resource Services team, offering guidance on a wide range of rare disease–related concerns. Support is available via phone or email, and a dedicated assistance line is offered for Spanish-speaking patients and families. Helpline staff provide reliable information, help navigate available services, and connect callers to appropriate resources, advocacy groups, and support programs.

NORD RareCare® Patient Assistance Programs

Offers financial assistance to help rare disease patients and families access essential care and resources. Many RareCare® Patient Assistance Programs are disease-specific, but the online database is updated regularly as new funding becomes available. Support may include help with medical expenses, travel costs to reach specialized treatment centers, and participation in clinical trials.

Caregivers can also apply for the Caregiver Respite Program, which provides funding to attend a conference, participate in educational opportunities, or take a restorative break from caregiving responsibilities.

NORD also offers the Rare Disease Educational Support Program, designed to help patients, families, and caregivers attend conferences or programs with rare disease–focused content.



NORD Support Helpline

Please call NORD at **1-800-469-0283** or email us at **informationservices@rarediseases.org**.

*Si deseas hablar con alguien en espanol por favor llame al **1-844-259-7178** para asistencia.*

VIII. Selected Published Medical Articles

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Brett Bordini, MD*
Children's Wisconsin/Medical College of Wisconsin

Jesse Hunter, PhD, FACMG*
Nationwide Children's Hospital/Ohio State University

Erin Baldwin, MS, CGC, MB (ASCP)
University of Utah Medical Genetics

Sara Berger, MS, CGC
Columbia University Irving Medical Center

Adam Brown, MD
Cleveland Clinic Center for Rare Diseases

Bimal Chaudhari, MD, MPH
Nationwide Children's Hospital/Ohio State University

Anna Hurst, MD, MS
UAB Medicine/Children's of Alabama

Sarah Jurgensmeyer, MS, CGC
NORD Rare Disease Center for Excellence at Ann & Robert H. Lurie Children's Hospital of Chicago and Northwestern University

Kristen N. Lee, MD
Michigan Medicine NORD Center of Excellence

Jaime Lopes, PhD
Cincinnati Children's Hospital Medical Center

Nifang Niu, MBBS, PhD
University of Iowa Health Care

Arti Pandya, MD
University of North Carolina Children's- North Carolina Children's Hospital/UNC Health

Dr. Nivedita Patni, MD
University of Texas Southwestern Medical Center

Amelle L. Shillington, DO
Cincinnati Children's Hospital Medical Center

Asha Talati, MD
University of North Carolina Children's- North Carolina Children's Hospital/UNC Health

Marwan Tayeh, PhD
Indiana University Health-Indiana University School of Medicine

Christie Thomas, MD
University of Iowa Health Care

Moon Ley Tung, MBBS
University of Iowa Health Care

Jaime Vengoechea, MD
Emory Division of Medical Genetics/Children's Healthcare of Atlanta

Francesco Vetrini, PhD
Indiana University Health-Indiana University School of Medicine

Bryn D. Webb, MD, FACMG
University of Wisconsin Center for Rare Diseases

Melissa Wright, MD
University of Colorado Anschutz Medical Campus/ Children's Hospital Colorado/ UC Health

Joseph Wu, MD, PhD
Stanford Medicine Children's Health-NORD Center of Excellence for Rare Disorders

*** Co-Chairs of the Diagnostic Approaches & Access to Testing Working Group**

NORD:

Gioconda Alyea, MD (IMG), MS, Medical Science Liaison and Ontoloy Specialist, Medical Affairs

Anjali Chauhan, Medical Affairs Program Manager

Alicia Lawrence, MSW, Patient Information Services

Marybeth McAfee, MA, GC, VP Community and Medical Affairs

Edward Neilan, MD, PhD, Chief Medical and Scientific Officer

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X. About NORD®

The National Organization for Rare Disorders (NORD®) was founded after the passage of the Orphan Drug Act of 1983, uniting the patient advocacy groups that helped make that landmark law a reality. Since then, NORD has remained a trusted national leader, dedicated to ensuring that people living with rare diseases, and those who care for them, feel seen, heard, supported, and connected.

As the first national nonprofit to represent all individuals and families affected by rare diseases, NORD continues to be the only organization working across care, research, and policy for the full rare disease community. We are a mission-driven, independent nonprofit reimagining a future where every person with a rare disease can live their best life.

Together with patients, families, clinicians, and researchers, we are united by a single purpose: to solve the greatest challenges in rare disease diagnosis, treatment, care, and research. Our organizational priorities and policy positions are shaped in partnership with our Board of Directors and member patient organizations, always with the best interests of patients and families in mind.

NORD accepts support from diverse sources, including government, industry, and individual donors, but remains firmly committed to transparency and independence. To avoid conflicts of interest, NORD does not allow employees of pharmaceutical or biotechnology companies to serve on its Board of Directors.

We are proud to stand at the center of the rare disease movement, championing progress, advancing equity, and building a stronger future for all rare disease communities.

View the full RareDx series on NORD's website rarediseases.org



XI. About the NORD Rare Disease Centers of Excellence Network

Launched in November 2021, the NORD Rare Disease Centers of Excellence Network is the first national network of U.S. academic medical centers dedicated to diagnosing, treating, and researching all rare diseases across the lifespan.

Modeled after successful networks built around individual or small groups of rare diseases, the NORD Centers of Excellence Program was created to extend the same benefits, including high-quality care, focused research, and better patient outcomes, to every person living with a rare disease, regardless of diagnosis.

Each designated NORD Rare Disease Center of Excellence was selected through a rigorous application process and recognized for:

- **Multidisciplinary care** through extensive array of specialists and subspecialists with expertise in diagnosing and managing a broad range of rare diseases in both children and adults.
- A deep **commitment to advancing rare disease research**, including studies aimed at understanding disease causes (etiology) and mechanisms (pathophysiology), improving diagnostic tools, and developing new treatments and potential cures.
- A shared mission to **training and mentorship** of the next generation of rare disease clinicians and scientists, actively involving fellows and junior faculty in clinical care, research, and training.

Beyond their local impact, each NORD Rare Disease Center of Excellence is part of a unified Network dedicated to collaboration and knowledge sharing, working together to improve care, accelerate discoveries, and solve some of the most challenging unmet needs in medicine.

The NORD Rare Disease Centers of Excellence Network is dedicated to:

- Diagnosing and treating thousands of rare disease patients nationwide
- Driving groundbreaking research and clinical innovation
- Providing mentorship and training to early-career healthcare professionals
- Creating a sustainable shared infrastructure for rare disease progress

At the heart of this program is NORD's commitment to ensuring that every rare disease patient has access to the expertise, care, and hope they deserve.

