

# GENETIC TESTING: EXOME AND GENOME SEQUENCING FOR THE DIAGNOSIS OF GENETIC DISORDERS

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## OVERVIEW

Exome sequencing (ES) (also known as ‘whole exome sequencing (WES)’) involves sequencing and often copy number variant (CNV) analysis of the portion of the genome that contains protein-coding DNA, which are termed exons. Together, all of the exons in a genome are known as the exome, which constitutes approximately 1% of the genome and is currently estimated to contain about 85% of heritable disease-causing variants.

Genome sequencing (GS) (also known as ‘whole genome sequencing (WGS)’) is a comprehensive method that sequences both coding and noncoding regions of the genome. GS has typically been limited to use in the research setting, but is emerging in the clinical setting and has a greater ability to detect large deletions or duplications in protein-coding regions compared with ES. GS requires greater data analysis but less DNA preparation prior to sequencing.

ES and GS have been proposed for use in patients presenting with disorders and anomalies not immediately explained by standard clinical workup. Potential candidates for ES and GS include patients who present with a broad spectrum of suspected genetic conditions.

Rapid exome sequencing (rES) and rapid genome (rGS) sequencing involves sequencing of the exome or genome, respectively, in an accelerated time frame. Preliminary results can typically be returned in less than 7 days, and a final report in less than two weeks. Studies suggest that the use of rES or rGS in acutely-ill infants, presenting with complex phenotypes that are likely rare genetic conditions, can identify a genetic diagnosis more quickly, allowing clinicians and family members to change acute medical or surgical management options and end the diagnostic odyssey. Ultra-rapid GS involves sequencing of the genome typically in less than 72 hours and is currently considered investigational.

## POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

<a href="#">Coverage Criteria Sections</a>	<b>Example Tests (Labs)</b>	<b>Common CPT Codes</b>	<b>Common ICD Codes</b>	<a href="#">Ref</a>
<a href="#">Standard Exome Sequencing</a>	Genomic Unity® Exome Plus Analysis - Proband (Variantyx Inc.)	0214U	F70-F79, F80.0-F89, Q00.0-Q99.9	1, 3, 4, 5, 6, 8, 9, 11, 12
	Genomic Unity® Exome Plus Analysis - Comparator (Duo or Trio) (Variantyx Inc.)	0215U		
	XomeDx - Proband (GeneDx)	81415		
	Exome - Proband Only (Invitae)			
	XomeDx - Duo (GeneDX)	81415, 81516		
	XomeDX - Trio (GeneDX)			
	Exome - Duo (Invitae)			
	Exome - Trio (Invitae)			
<a href="#">Rapid Exome Sequencing</a>	XomeDxXpress (GeneDx)	81415, 81416	F70-F79, F80-F89, Q00.0-Q99.9	7, 9
	ExomeNext-Rapid (Ambry)			
	Rapid PGxome (PreventionGenetics)			
	STAT Whole Exome Sequencing (PerkinElmer Genomics)			
<a href="#">Standard Genome Sequencing</a>	Genomic Unity® Whole Genome Analysis - Proband (Variantyx Inc.)	0212U	F70-F79, F80-F89, Q00.0-Q99.9	10
	Genomic Unity® Whole Genome Analysis - Comparator (Variantyx Inc.)	0213U		
	GenomeSeqDx (GeneDx)	81425, 81426		
	TruGenome Trio (Illumina)			
	Whole Genome Sequencing (PerkinElmer Genomics)			

	MNGenome (MNG Laboratories)			
	CNGenome (PerkinElmer Genomics)	0209U		
	Praxis Whole Genome Sequencing (Praxis Genomics LLC)	0265U		
	Praxis Combined Whole Genome Sequencing and Optical Genome Mapping (Praxis Genomics LLC)	0267U		
<a href="#">Rapid Genome Sequencing</a>	Rapid Whole Genome Sequencing (Rady Children’s Institute for Genomic Medicine)	0094U	F70-F79, F80-F89, Q00.0-Q99.9	2
	Ultra-Rapid Whole Genome Sequencing (Rady Children’s Institute for Genomic Medicine)	81425, 81426		
	STAT Whole Genome Sequencing (PerkinElmer Genomics)			
	MNGenome STAT (Labcorp/MNG Laboratories)			

## OTHER RELATED POLICIES

This policy document provides coverage criteria for exome and genome sequencing for the diagnosis of genetic disorders in patients with suspected genetic disorders and for population-based screening. Please refer to:

- **Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies** for coverage criteria related to exome and genome sequencing of solid tumors and hematologic malignancies.
- **Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay** for coverage criteria related to diagnostic genetic testing performed after a child has been born.

- **Genetic Testing: Prenatal and Preconception Carrier Screening** for coverage criteria related to prenatal carrier screening, preimplantation genetic testing, or preconception carrier screening.
- **Genetic Testing: Prenatal Diagnosis (via Amniocentesis, CVS, or PUBS) and Pregnancy Loss** for coverage related to prenatal exome sequencing.
- **Genetic Testing: General Approach to Genetic Testing** for coverage criteria related to exome and genome sequencing that is not specifically discussed in this or another non-general policy.

## COVERAGE CRITERIA

### STANDARD EXOME SEQUENCING

- I. Standard exome sequencing (81415, 81416, 0214U, 0215U), with [trio testing](#) when possible, is considered **medically necessary** when:
  - A. The member meets one of the following:
    1. The member has unexplained epilepsy at any age, **OR**
    2. The etiology of the member's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on **EITHER** of the following:
      - a) The member has apparently nonsyndromic [developmental delay](#) or [intellectual disability](#) with onset prior to age 18 years, **OR**
      - a) Multiple congenital abnormalities affecting unrelated organ systems, **OR**
      - b) **TWO** of the following criteria are met:
        - (1) Abnormality significantly affecting (at minimum) a single organ system, **OR**
        - (2) Dysmorphic features, **OR**

- (3) Encephalopathy, **OR**
  - (4) Symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity/hypertonia, epilepsy, hypotonia), **OR**
  - (5) Family history strongly suggestive of a genetic etiology, including consanguinity, **OR**
  - (6) Clinical or laboratory findings suggestive of an inborn error of metabolism, **AND**
- B. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
  - C. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**
  - D. A diagnosis cannot be made in a timely manner by standard clinical evaluation, excluding invasive procedures such as muscle biopsy, **AND**
  - E. There is a predicted impact on the health outcome, including impact on medical management during the hospitalization based on the results, **AND**
  - F. Pre- and post-test counseling by an appropriate provider, such as a Board-Certified Medical Geneticist, a Certified Genetic Counselor, or an Advanced Practice Nurse in Genetics, **AND**
  - G. The patient and patient's family history have been evaluated by a Board Certified or Board-Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN).
- II. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) for the above indications may be considered **medically necessary** when:
- A. Significant new symptoms develop in the member or the member's family history, **AND**
  - B. The member has been re-evaluated by a Board-Certified or Board-Eligible Medical Geneticist, a Certified Genetic Counselor, an advanced practice practitioner (e.g. APRN or Physician's Assistant) in genetics, who is not

employed by a commercial genetic testing laboratory that recommends repeat exome sequencing, **AND**

- C. There have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or new information regarding the genetic etiology of a condition that could explain the patient's clinical features and would not have been able to be detected by the previous exome sequencing.
- III. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **not medically necessary** for all other indications.
- IV. Standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

[back to top](#)

## RAPID EXOME SEQUENCING

- I. Rapid exome sequencing (81415, 81416) is considered **medically necessary** when:
  - A. The member is an acutely-ill infant (12 months of age or younger), **AND**
  - B. The patient and patient's family history have been evaluated by a Board-Certified or Board-Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), **AND**
  - C. The etiology of the infant's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on **EITHER** of the following:
    - 1. Multiple congenital abnormalities affecting unrelated organ systems, **OR**
    - 2. **TWO** of the following criteria are met:

- a) Abnormality significantly affecting at minimum a single organ system, **OR**
  - b) Dysmorphic features, **OR**
  - c) Encephalopathy, **OR**
  - d) Dysmorphic features, **OR**
  - e) Symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia), **OR**
  - f) Family history strongly suggestive of a genetic etiology, including consanguinity, **OR**
  - g) Clinical or laboratory findings suggestive of an inborn error of metabolism, **AND**
- D. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
- E. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**
- F. A diagnosis cannot be made in a timely manner by standard clinical evaluation, excluding invasive procedures such as muscle biopsy, **AND**
- G. There is a predicted impact on the health outcome, including impact on medical management during the hospitalization based on the results, **AND**
- H. Pre- and post-test counseling by an appropriate provider, such as a Board-Certified Medical Geneticist, a Certified Genetic Counselor, or an Advanced Practice Nurse in Genetics, **AND**
- I. The acutely-ill infant does **not** have any of the following diagnoses:
- 1. Isolated Transient Neonatal Tachypnea
  - 2. Isolated unconjugated hyperbilirubinemia
  - 3. Isolated Hypoxic Ischemic Encephalopathy with clear precipitating event
  - 4. Isolated meconium aspiration

- II. Rapid exome sequencing (81415, 81416) is considered **investigational** for all other indications.

[back to top](#)

## STANDARD GENOME SEQUENCING

- I. Standard genome sequencing (81425, 81426, 0209U, 0212U, 0213U, 0265U, 0267U) is considered **investigational**.

[back to top](#)

## RAPID GENOME SEQUENCING

- I. Rapid genome sequencing (81425, 81426, 0094U) is considered **medically necessary** when:
  - A. The member is an acutely-ill infant (12 months of age or younger), **AND**
  - B. The patient and patient's family history have been evaluated by a Board-Certified or Board-Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), **AND**
  - C. The etiology of the infant's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on **EITHER** of the following:
    1. Multiple congenital abnormalities affecting unrelated organ systems, **OR**
    2. **TWO** of the following criteria are met:
      - a) Abnormality significantly affecting at minimum a single organ system, **OR**
      - b) Encephalopathy, **OR**



- c) Symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia), **OR**
  - d) Family history strongly suggestive of a genetic etiology, including consanguinity, **OR**
  - e) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**
  - f) Abnormal response to therapy, **AND**
- D. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
- E. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted panel testing is available, **AND**
- F. rGS is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity), **AND**
- G. A diagnosis cannot be made in a timely manner by standard clinical evaluation, excluding invasive procedures such as muscle biopsy, **AND**
- H. There is a predicted impact on health outcomes, including immediate impact on medical management during the hospitalization based on the results , **AND**
- I. Pre- and post-test counseling by an appropriate provider, such as a Board-Certified Medical Geneticist, a Certified Genetic Counselor, or an Advanced Practice Nurse in Genetics, **AND**
- J. The acutely-ill infant does **not** have any of the following diagnoses:
1. Isolated Transient Neonatal Tachypnea
  2. Isolated unconjugated hyperbilirubinemia
  3. Isolated Hypoxic Ischemic Encephalopathy with clear precipitating event
  4. Isolated meconium aspiration

- II. Rapid genome sequencing (81425, 81426, 0094U) is considered **investigational** for all other indications.

[back to top](#)

## NOTES AND DEFINITIONS

**Exome Sequencing (ES)** is a genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).

**Genome Sequencing (GS)** is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

**Trio Testing** includes testing of the child and both biological/genetic parents and increases the chances of finding a definitive diagnosis, while reducing false-positive findings.

**Comparator Exome Sequencing** is used only for comparison with the proband (individual undergoing exome sequencing) and is used to inform the pathogenicity of variants. A comparator exome is typically one or both biological/genetic parents to the proband.

**Congenital anomalies** according to ACMG are multiple anomalies not specific to a well-delineated genetic syndrome. These anomalies are structural or functional abnormalities usually evident at birth, or shortly thereafter, and can be consequential to an individual's life expectancy, health status, physical or social functioning, and typically require medical intervention.

**Developmental delay** is a slow-to-meet or not reaching milestones in one or more of the areas of development (communication, motor, cognition, social-emotional, or adaptive skills) in the expected way for a child's age

**Intellectual disability (ID)** is defined by the DSM-V as:

- a. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing.
- b. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social

responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community.

- c. Onset of intellectual and adaptive deficits during the developmental period.

[back to top](#)

## CLINICAL CONSIDERATIONS

Trio testing is preferred whenever possible. Testing of one available parent is a valid alternative if both are not immediately available and one or both parents can be done later if needed. While trio sequencing is preferred and recommended, an alternative method referred to as “Patient Plus” by PreventionGenetics may be considered. “Patient Plus” involves sequencing and copy number variant (CNV) analysis of the patient, and then targeted testing for the key variants found in the patient is performed on parental specimens. This approach permits detection of de novo variants and phasing of variants in recessive genes to increase diagnostic yield from a singleton sample in situations where full trio sequencing may not be feasible or preferable.

Exome sequencing or genome sequencing can reveal incidental findings or secondary findings. These findings are defined as results that are not related to the indication for undergoing the sequencing, but may be of medical value or utility. Disclosure of these findings has been a topic of intense debate within the medical genetics community. In 2013, ACMG published recommendations for reporting secondary findings that included a list of conditions to be included. The list currently includes 59 genes that confer highly-penetrant and medically actionable conditions.

Pre-test and post-test genetic counseling that facilitates informed decision-making, the possibility to identify secondary finding with the option to ‘opt out’ of receiving these results, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs is strongly advised.

If a genetic diagnosis is not found by ES or GS, periodic reanalysis of the previously obtained genomic sequence is recommended. Reevaluation can occur on the variant-level or case-level. When appropriate, retesting may be considered (see above). Any variants

identified and reported prior to the current ACMG variant classification standards should be reevaluated using the current ACMG standards.

Variant-level reanalysis should be considered in the following circumstances:

- Availability of a new community resource (e.g., gnomAD)
- Publication and/or adoption of a novel/updated methodology for variant assessment
- Publication of evidence supporting new gene–disease relationships and/or mechanisms of disease

Case-level reanalysis should be considered in the following circumstances:

- Significant changes in clinical and family history occur
- Significant improvements have been made to the bioinformatics handling of the data

[back to top](#)

## BACKGROUND AND RATIONALE

### Standard Exome Sequencing

*American College of Medical Genetics and Genomics (ACMG)*

In 2021, ACMG published an evidence-based clinical practice guideline on exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability (Manickam, 2021).

- ACMG recommends using exome or genome sequencing as a first- or second-tier test for patients diagnosed with one or more congenital anomalies before the age of 1, or with intellectual disability/developmental delay before the age of 18. (p. 2031)
- ACMG recommends exome or genome sequencing for active and long-term clinical management of the proband, as well as for implications on family-focused and reproductive outcomes. (p. 2032)
- These guidelines also recommend consideration of exome sequencing after the results of chromosome microarray or focused genetic testing are uninformative for a patient with one or more congenital anomaly or patients with developmental delay/intellectual disability. (p. 2031)

ACMG also released a systematic evidence-based review (Malinowski, 2020) of 167 published studies examining the clinical impact of exome sequencing (ES) and genome sequencing (GS) in individuals with congenital anomalies (CA), developmental delay (DD), and intellectual disability (ID). This systematic review “provide[d] indirect evidence of the clinical and personal utility of ES/GS for patients with CA/DD/ID and their family members,” noting that a “change in clinical management” resulted in over half of the patients examined as a result of their ES/GS results.

In regards to repeat exome sequencing, ACMG published a statement in 2019 recommending that repeat testing be considered when significant changes occur in the patient’s personal and/or family histories, or if there have been improvements in testing methodologies, ability to analyze data, or understanding of the genetic etiology of disease (p. 1296) (Deignan, 2019).

In 2022, ACMG published ACMG SF v3.1, an updated list of genes included in the secondary findings (SF), which added an additional 5 genes bringing the total up to 78 genes (Miller, Lee, Gordon, 2021). ACMG also published a policy statement regarding updated recommendations for reporting of secondary findings in clinical exome and genome sequencing, which clarified that ACMG supports the continued research and discussion around population screening for the genes included in the secondary findings list. However, “ACMG has made it clear that the ACMG SF is not validated for general population screening” (Miller, Lee, Chung, 2021).

#### *National Society for Genetic Counselors*

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020) stating the following in regard to secondary and incidental findings in genetic testing:

“The National Society of Genetic Counselors strongly advises pre-test counseling that facilitates informed decision-making, elicits patient preferences regarding secondary and/or incidental findings if possible, and formulates a plan for returning such results before testing occurs.

Germline and somatic genetic testing, in both clinical and research contexts, may identify secondary findings and incidental findings as a part of the test performed. Secondary findings are purposely analyzed as part of the test, but unrelated to the primary testing indication. Incidental findings are detected unexpectedly during the analysis, and also unrelated to the primary testing indication. Both of these types of variants may be disclosed as a part of the return-of-results process.

The pre-test counseling process should establish clear expectations for what categories of results will and will not be returned. Healthcare practitioners conducting the informed consent and return-of-results processes for broad genomic testing and screening should ensure that their patients have access to practitioners with genetic expertise, such as genetic counselors.”

### *UpToDate*

UpToDate is an evidence-based clinical decision support resource that is expert-authored and goes through a multi-layered review and consensus process.

### Intellectual disability in children: Evaluation for a cause

“Whole exome sequencing — WES should be considered for patients with moderate to severe ID in whom other standard tests (including CMA) have failed to identify the cause. The diagnostic yield of WES in this setting is approximately 16 to 33 percent. The diagnostic yield is likely lower in patients with mild ID without additional findings and the role of WES testing in this population is not defined. WES testing should be performed with consultation of a clinical geneticist and should include appropriate pretest counseling to discuss the risk of incidental findings unrelated to the child's ID that may be medically actionable (eg, BRCA1 or BRCA2 mutation). Incidental findings can be minimized if a focused analysis is conducted. Due to the falling costs of sequencing and its high diagnostic yield, WES is rapidly becoming a clinical tool for the evaluation of ID, especially at specialty centers. Adoption of WES testing into the diagnostic process will depend on its cost, availability, access to expert interpretation, and the allocation of resources within each health care setting.”

### *National Society of Genetic Counselors*

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (Smith et al, 2022). The NSGC recommendations are as follows (p. 4):

- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age.
- Multi-gene, comprehensive testing, such as exome sequencing, genome sequencing or a multigene panel as a first-tier test is strongly recommended

### *Patient-centered Laboratory Utilization Guidance (PLUGS)*

PLUGS developed an expert-written exome sequencing coverage policy as part of their insurance alignment focus. Their policy includes the following criteria for exome sequencing:

- The patient and family history have been evaluated by a Board -Certified or Board -Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC )  
**AND**
- A genetic etiology is considered the most likely explanation for the phenotype, based on EITHER of the following **AND**
  - Multiple congenital abnormalities affecting unrelated organ systems
  - **TWO** of the following criteria are met:
    - abnormality affecting at minimum a single organ system significant neurodevelopmental disorder (e.g., global developmental delay, intellectual disability , and/or period of unexplained developmental regression )
    - symptoms of a complex neurological condition (e.g. , dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy )
    - severe neuropsychiatric condition (e.g. , schizophrenia, bipolar disorder, Tourette syndrome, self -injurious behavior, reverse sleep -wake cycles )
    - family history strongly suggestive of a genetic etiology, including consanguinity
    - laboratory findings suggestive of an inborn error of metabolism
- Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection), **AND**
- Clinical presentation does not fit a well -described syndrome for which single - gene or targeted panel testing (e.g., comparative genomic hybridization [CGH]/chromosomal microarray analysis [CMA]) is available, **AND**
- WES is more efficient and economical than the separate single -gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity), **AND**
- A diagnosis cannot be made by standard clinical work -up, excluding invasive procedures such as muscle biopsy, **AND**
- Predicted impact on health outcomes, as above, **AND**

- Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), such as an American Board of Medical Genetics or American Board of Genetic Counseling -certified Genetic Counselor

## Rapid Exome Sequencing

*Kingsmore SF, Cakici JA, Clark MM et al. 2019*

This report is from the NSIGHT2 study, a prospective randomized, controlled, blinded trial (RCT) in acutely ill infants, primarily from the NICU, PICU, and CVICU at Rady Children’s Hospital, San Diego (RCHSD) to compare the effectiveness and outcomes between rWGS and rWES, with analysis as singleton probands and familial trios. The inclusion criteria for the 1,248 ill infants defined the maximum age at the time of admission as four months. They found that 24% of infants undergoing rapid exome sequencing had genetic disease. They conclude that diagnostic testing in infants with diseases of unknown etiology, rapid genomic sequencing, including rapid exome sequencing can be performed as a first tier test in infants with diseases of unknown etiology at time of admission to ICUs. In unstable infants and in those whom a genetic diagnosis was likely to impact immediate management, rapid genomic sequencing had optimal analytic and diagnostic performance by virtue of shortest time to results. (p. 725)

*Patient-centered Laboratory Utilization Guidance (PLUGS)*

The PLUGS Exome Sequencing policy acknowledges that exome sequencing “is typically not an appropriate first -tier test, but can be appropriate if initial testing is unrevealing, or if there is no single-gene or panel test available for the particular condition, or if a rapid diagnosis for a critically-ill child is indicated.” (p. 1)

## Standard Genome Sequencing

*American College of Medical Genetics and Genomics (ACMG) 2021 revision on Next-generation sequencing for constitutional variants in the clinical laboratory states the following:*

“... Exome Sequencing or Genome Sequencing provide[s] a broad approach to match detected variants with the clinical phenotype assessed by the laboratory and health-care provider. Exome Sequencing may be performed with the intention of restricting



interpretation and reporting to variants in genes with specific disease associations with an option to expand the analysis to the rest of the exome if the initial analysis is nondiagnostic. Exome Sequencing/Genome Sequencing approaches are most appropriate in the following scenarios: (1) when the phenotype is complex and genetically heterogeneous; (2) when the phenotype has unusual features, an atypical clinical course, or unexpected age of onset; (3) when the phenotype is associated with recently described disease genes for which disease-targeted testing is unavailable; (4) when focused testing has been performed and was nondiagnostic; (5) when sequential testing could cause therapeutic delays; or (6) when the phenotype does not match an identified genetic condition, suggesting the possibility of more than one genetic diagnosis, which has been documented in 4–7% of positive cases. When Exome Sequencing/Genome Sequencing does not establish a diagnosis, the data can be reanalyzed (section E.6). The potential impact of secondary findings with Exome Sequencing/Genome Sequencing should also be considered (section E.3).” (p. 1400-1401)

## Rapid Genome Sequencing

### *Patient-centered Laboratory Utilization Guidance (PLUGS)*

PLUGS developed an expert-written rapid genome sequencing coverage policy as part of their insurance alignment focus. This policy references multiple primary research publications with examples of clinical presentations that result in evidence of clinical utility. (p. 3)

They recommend rapid whole genome testing criteria to include acutely ill infants 12 months of age or younger whose features suggest an unknown genetic etiology and have a complex phenotype which may include a combination of multiple congenital anomalies, encephalopathy, symptoms of a complex neurodevelopmental disorder, family history suggestive of genetic etiology, laboratory findings suggestive of an inborn error of metabolism and an abnormal response to therapy. The clinical presentation should not fit a well-described syndrome for which rapid single gene or targeted panel testing is available. They suggest that there should be predicted impact on health outcomes, including immediate impact on medical management based on the molecular results. (p. 3-4)

[back to top](#)

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[back to top](#)