

# 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 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. GS has been shown to have a higher diagnostic yield compared to ES when used as a first line test. ES reanalysis is often performed approximately 18 months to 2 years following initial, uninformative ES. Studies have shown that the diagnostic yield of ES reanalysis is comparable to performing GS after an uninformative ES.

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.

## POLICY REFERENCE TABLE

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the [Concert Genetics Platform](#) for a comprehensive list of registered tests.

<a href="#">Coverage Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	<a href="#">Ref</a>
<a href="#">Standard Exome Sequencing</a>	Genomic Unity Exome Plus Analysis - Proband (Variantyx)	0214U	F70-F79, F80.0-F89, Q00.0-Q99.9	1, 3, 5, 7, 8, 11, 12, 13
	Genomic Unity Exome Plus Analysis - Comparator (Duo or Trio) (Variantyx Inc.)	0215U		
	XomeDx - Proband (GeneDx)	81415		
	Exome - Proband Only (Invitae)			
	XomeDx - Duo (GeneDx)	81415, 81416		
	XomeDX - Trio (GeneDx)			
	Exome - Duo (Invitae)			
	Exome - Trio (Invitae)			
<a href="#">Reanalysis of Exome or Genome Sequencing Data</a>	Exome Reanalysis (Ambry)	81417	F70-F79, F80-F89, Q00.0-Q99.9	4, 9, 10, 12
	Whole Genome Reanalysis (ARUP)	81427		
<a href="#">Rapid Exome Sequencing</a>	XomeDxXpress (GeneDx)	81415, 81416	F70-F79, F80-F89, Q00.0-Q99.9	1, 3, 5, 6, 7, 8, 11, 12, 13
	ExomeNext-Rapid (Ambry)			
	PGxome RAPID Exome Test (PreventionGenetics, part of Exact Sciences)			

	STAT Whole Exome Sequencing (PerkinElmer Genomics)			
<a href="#">Standard Genome Sequencing</a>	Genomic Unity Whole Genome Analysis - Proband (Variantx Inc.)	0212U	F70-F79, F80-F89, Q00.0-Q99.9	1, 3, 5, 7, 8, 11, 12, 13
	Genomic Unity® Whole Genome Analysis - Comparator (Variantx Inc.)	0213U		
	GenomeSeqDx (GeneDx)	81425, 81426		
	TruGenome Trio (Illumina)			
	Whole Genome Sequencing (PerkinElmer Genomics)			
	MNGenome (MNG Laboratories)			
	Praxis Whole Genome Sequencing (Praxis Genomics LLC)	0265U		
<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, 3, 6, 8, 11
	Rapid Whole Genome Sequencing, Comparator Genome (Rady Children’s Institute for Genomic Medicine)	0425U		
	Ultra-Rapid Whole Genome Sequencing (Rady Children’s Institute for Genomic Medicine)	0426U		
	STAT Whole Genome Sequencing (PerkinElmer Genomics)	81425, 81426		
	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 and Molecular 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 has not previously had genome sequencing, **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. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**
- E. The member meets at least one of the following clinical findings:
  - 1. The member has unexplained epilepsy diagnosed at any age, **OR**
  - 2. The member has [global developmental delay](#) or [intellectual disability](#) with onset prior to age 18 years, **OR**
  - 3. The member was diagnosed with at least one [congenital anomaly](#) (functional and/or structural), **OR**
  - 4. The member has at least **TWO** of the following:
    - a) Bilateral sensorineural hearing loss of unknown etiology, **OR**
    - b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**
    - c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
    - d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**
    - e) Autism, **OR**
    - f) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**
    - g) Period of unexplained developmental regression (unrelated to epilepsy or autism).

- II. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational**.
- III. Standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

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## REANALYSIS OF EXOME OR GENOME SEQUENCING DATA

- I. Reanalysis of exome or genome sequencing data (81417, 81427) is considered **medically necessary** when\*:
  - A. The member had exome or genome sequencing at least 18 months ago, **OR**
  - B. The member's phenotype has expanded to include clinical findings\*\* that were not present at the time of the initial exome or genome sequencing analysis, **AND**
    - 1. Results of prior exome or genome sequencing do not explain these new clinical findings.
- II. Reanalysis of exome or genome sequencing data (81417, 81427) is considered **investigational** for all other indications.

\*If reanalysis of exome data is not possible, see the genome sequencing criteria for additional coverage information.

\*\*See [Standard Exome Sequencing](#) or [Standard Genome Sequencing](#) criteria for qualifying clinical findings.

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## RAPID EXOME SEQUENCING

- I. Rapid exome sequencing (81415, 81416), with [trio testing](#) when possible, is considered **medically necessary** when:
  - A. The member is an acutely-ill infant (12 months of age or younger), **AND**
  - B. The member has not previously had genome sequencing, **AND**
  - C. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
  - D. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**
  - E. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**
  - F. The member meets at least one of the following clinical findings:
    1. The member has unexplained epilepsy , **OR**
    2. The member has [global developmental delay](#), **OR**
    3. The member was diagnosed with at least one [congenital anomaly](#) (functional and/or structural), **OR**
    4. The member has at least **TWO** of the following:
      - a) Bilateral sensorineural hearing loss of unknown etiology, **OR**
      - b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, myopathy, muscular dystrophy), **OR**
      - c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
      - d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**

- e) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**
  - f) Period of unexplained developmental regression (unrelated to epilepsy or autism).
- II. Rapid exome sequencing (81415, 81416) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

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## STANDARD GENOME SEQUENCING

- I. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **medically necessary** when:
- A. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**
  - B. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**
  - C. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**
  - D. The member meets at least one of the following clinical findings:
    - 1. The member previously had uninformative exome sequencing (ES), **AND**
      - a) [ES reanalysis is not possible](#), **OR**
    - 2. The member has unexplained epilepsy diagnosed at any age, **OR**
    - 3. The member has [global developmental delay](#) or [intellectual disability](#) with onset prior to age 18 years, **OR**

4. The member was diagnosed with at least one [congenital anomaly](#) (functional and/or structural), **OR**
5. The member has at least **TWO** of the following:
  - a) Bilateral sensorineural hearing loss of unknown etiology, **OR**
  - b) Symptoms of a complex neurological disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, myopathy, muscular dystrophy), **OR**
  - c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
  - d) Clinical or laboratory findings suggestive of an inborn error of metabolism, **OR**
  - e) Autism, **OR**
  - f) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**
  - g) Period of unexplained developmental regression (unrelated to epilepsy or autism).
- II. Repeat standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational**.
- III. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

**Note:** When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.

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## RAPID GENOME SEQUENCING

- I. Rapid genome sequencing (rGS) (81425, 81426, 0094U, 0425U, 0426U), with [trio testing](#) when possible, is considered **medically necessary** when:
  - A. The member is an acutely-ill infant (12 months of age or younger), **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. The member's personal and family histories have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN), **AND**
  - E. The member meets at least one of the following clinical findings:
    1. The member has multiple [congenital abnormalities](#) (functional and/or structural) affecting unrelated organ systems, **OR**
    2. The member has epileptic encephalopathy, **OR**
    3. The member has at least **TWO** of the following:
      - a) Abnormality affecting at least one organ system, **OR**
      - b) Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global [developmental delay](#), [intellectual disability](#)), **OR**
      - c) Family history suggestive of a genetic etiology, including consanguinity, **OR**
      - d) Laboratory findings suggestive of an inborn error of metabolism, **OR**
      - e) Abnormal response to standard therapy.

- II. Rapid genome sequencing (rGS) (81425, 81426, 0094U, 0425U, 0426U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

**Note:** When genome sequencing is performed, the mitochondrial genome is assumed to be included as a part of the analysis.

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## DEFINITIONS

1. **Exome Sequencing (ES):** A genomic technique for sequencing all of the protein-coding regions of genes in the genome (also known as the exome).
2. **Genome Sequencing (GS):** A genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.
3. **Trio Testing:** Testing of the child and both biological/genetic parents and increases the chances of finding a definitive diagnosis, while reducing false-positive findings.
4. **Comparator Exome Sequencing:** 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.
5. **Congenital anomalies:** According to ACMG, congenital anomalies 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.
6. **Global Developmental delay:** An individual that is slow-to-meet or not reaching milestones in the expected way for a child's age in at least two of the areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills) **Intellectual disability (ID):** 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.
7. **Exome sequencing (ES) reanalysis** may not be possible in some situations. Sequencing platforms may have changed substantially enough that the performing lab can no longer use the data from the original ES in their pipeline. Specifically, ES reanalysis may not be possible if there have been improvements in technology/chemistry (e.g., new methods for DNA capture and/or sequencing), bioinformatics advancements, or there is 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.

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

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## 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), which included the following:

- 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 for patients 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)

Of note, ACMG states that “Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing.” (p. 2034)

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. (p. 1001)

In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

#### *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”

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 Services*

In the PLUGS July 2023 guidelines entitled “Genomic Sequencing for Rare Disease,” the following clinical criteria are recommended, in part, for exome sequencing and genome sequencing.

“Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met: ...

1. The etiology of the patient’s features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on... the following...
  - a. Epilepsy of unexplained etiology with onset at any age, OR
  - b. Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
  - c. Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
  - d. Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
  - e. Multiple congenital anomalies affecting unrelated organ systems, OR
  - f. At least TWO of the following criteria are met:
    - i. Abnormality affecting at minimum a single organ system
    - ii. Autism
    - iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
    - iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)
    - v. Family history strongly suggestive of a genetic etiology, including consanguinity
    - vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
    - vii. Laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.” (p. 7)

### *Rehm et al (2023)*

Traditional genetic testing strategies have included single gene analysis or multi-gene panels as a first line test, which may still be the most appropriate test for a patient. However, there is increasing evidence that exome or genome sequencing may be more elucidating options. A 2023 paper by Rehm et al on behalf of the Medical Genome Initiative, which analyzed the rate of variants of uncertain significance (VUS) in 1,463,812 multigene panels, 42,165 exome sequencing tests, and 6,329 genome sequencing tests across 19 North American clinical laboratories, demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%). (p. 5 and 6)

### *Belanger, et al*

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

- Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living. (p. 404)

## **Reanalysis of Exome or Genome Sequencing Data**

### *Tan, et al*

A study from 2020 examined data from 58 unsolved cases referred for any indication to evaluate the systematic reanalysis of singleton exome sequencing (ES). The authors performed a reanalysis at multiple timepoints following initial testing, and ultimately suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis. (p. 1)

### *Alfares, et al.*

This study from 2018 compared the detection rates of whole-exome sequencing (WES) and whole-genome sequencing (WGS) in a clinical setting. The study included 108 patients with negative array CGH and negative or inconclusive WES results. WGS was performed on all patients, and the results of the study showed that 30% of the positive

cases identified by WGS could be identified by reanalyzing WES raw data, and WGS achieved an only 7% higher detection rate. (p. 1328) The paper concluded that, although WGS is a more powerful tool than WES, in this study, “we showed that WGS has additional, but limited, clinical utility compared with reanalyzing WES data, and until the cost of WGS approximates that of WES, reanalyzing WES raw data is recommended before performing WGS.” (p. 1333)

#### *American College of Medical Genetics*

A statement from ACMG (Deignan, 2019) included considerations for case-level exome re-analysis, which include the following:

- Significant improvements have been made to bioinformatics handling of the data (alignment/variant calling and/or the automated filtering processes)
- Updated clinical and family history information, which may result in the identification of additional variants that are associated with the indication(s) for testing. (p. 1269)

#### *Patient-Centered Laboratory Utilization Guidance Services*

The PLUGS July 2023 guidelines entitled “Genomic Sequencing for Rare Disease” state the following regarding reanalysis of exome or genome sequencing data: “Periodic reanalysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. A review of twenty-seven peer-reviewed articles revealed a median new diagnosis rate via reanalysis of 15% and median reanalysis timeframe of 22 months. The authors suggest that an interval of greater than 18 months from the original report may be optimal for reanalysis.” (p. 3)

The guidelines also state: “Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. Re-analysis could be considered prior to additional genomic sequencing, particularly if there has been onset or identification of additional symptoms that broadens the clinical phenotype assessed during the original ES/GS analysis...” (p. 8)

## Rapid 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), which included the following:

- 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 for patients 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)

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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. (p. 1001)

In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

### *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.”

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 Services*

In the PLUGS July 2023 guidelines entitled “Genomic Sequencing for Rare Disease,” the following clinical criteria are recommended, in part, for exome sequencing and genome sequencing.

“Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met: ...

1. The etiology of the patient’s features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on... the following...
  - a. Epilepsy of unexplained etiology with onset at any age, OR
  - b. Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
  - c. Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
  - d. Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major

- developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
- e. Multiple congenital anomalies affecting unrelated organ systems, OR
  - f. At least TWO of the following criteria are met:
    - i. Abnormality affecting at minimum a single organ system
    - ii. Autism
    - iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
    - iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)
    - v. Family history strongly suggestive of a genetic etiology, including consanguinity
    - vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
    - vii. Laboratory findings suggestive of an inherited metabolic disorder
- 2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
  - 3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.” (p. 7)

*Rehm et al (2023)*

Traditional genetic testing strategies have included single gene analysis or multi-gene panels as a first line test, which may still be the most appropriate test for a patient. However, there is increasing evidence that exome or genome sequencing may be more elucidating options. A 2023 paper by Rehm et al on behalf of the Medical Genome Initiative, which analyzed the rate of variants of uncertain significance (VUS) in 1,463,812 multigene panels, 42,165 exome sequencing tests, and 6,329 genome sequencing tests across 19 North American clinical laboratories, demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%). (p. 5 and 6)

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*Belanger, et al*

A review of the evaluation of children with global developmental delay and intellectual disability by Belanger et al (2018) defines global developmental delay (GDD) as the following:

- Significant delay (at least 2 standard deviations below the mean) in at least two developmental domains (gross or fine motor, speech/language, cognition, social/personal or activities of daily living. (p. 404)

## **Standard Genome 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), which included the following:

- 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 for patients 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)

Of note, ACMG states that “Isolated autism without ID or congenital malformation is formally out of scope for this recommendation but evaluation of exome/genome studies is ongoing.” (p. 2034)

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. (p. 1001)

In their clinical practice resource for the clinical evaluation of hearing loss published in 2022 by Li et al, ACMG states that first-line genetic testing for individuals with exam findings that suggest a syndromic hearing loss etiology may include a variety of tests, including genome sequencing, depending on clinical presentation. For individuals without physical findings that suggest a syndromic hearing loss etiology, they recommend a tiered approach, starting with comprehensive hearing loss gene panel testing unless a more specific genetic etiology is evident for which targeted testing is appropriate. (p. 1400)

### *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.”

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 Services*

In the PLUGS July 2023 guidelines entitled “Genomic Sequencing for Rare Disease,” the following clinical criteria are recommended, in part, for exome sequencing and genome sequencing.

“Exome sequencing or genome sequencing (ES/GS) is considered medically necessary when ALL of the following criteria are met: ...

1. The etiology of the patient’s features is not known, and a genetic etiology is considered a likely explanation for the phenotype, based on... the following...
  - a. Epilepsy of unexplained etiology with onset at any age, OR
  - b. Confirmed bilateral sensorineural hearing loss of unknown etiology and panel testing is unrevealing, OR
  - c. Intellectual disability, following formal assessment by a developmental pediatrician or neurologist, defined as moderate/severe/profound by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosed by 18 years of age, OR
  - d. Global developmental delay, following formal assessment by a developmental pediatrician or neurologist, defined as significant delay in younger children, under age five years, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living, OR
  - e. Multiple congenital anomalies affecting unrelated organ systems, OR
  - f. At least TWO of the following criteria are met:
    - i. Abnormality affecting at minimum a single organ system
    - ii. Autism
    - iii. Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles)
    - iv. Symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, hypotonia, myopathy, muscular dystrophy)

- v. Family history strongly suggestive of a genetic etiology, including consanguinity
  - vi. Period of unexplained developmental regression (unrelated to epilepsy or autism)
  - vii. Laboratory findings suggestive of an inherited metabolic disorder
2. Alternate etiologies have been considered and ruled out, when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.” (p. 7)

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## **Rapid Genome Sequencing**

### *Patient-Centered Laboratory Utilization Guidance Services*

In the PLUGS June 2022 guidelines entitled “Rapid Genome Sequencing,” the following clinical criteria are recommended for coverage for “acutely-ill individuals” who meet “ALL of the following criteria”:

“1. The etiology of the patient’s features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on one of the following

a) Multiple congenital abnormalities affecting unrelated organ systems, OR

b) Epileptic encephalopathy, OR

c) TWO of the following criteria are met:

- abnormality affecting at minimum a single organ system
- symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global developmental delay, intellectual disability)
- family history strongly suggestive of a genetic etiology, including consanguinity
- laboratory findings suggestive of an inborn error of metabolism
- abnormal response to standard therapy

2. Alternate etiologies have been considered and ruled out when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND

3. 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)...” (p. 3 and 4)

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