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

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. Ultra-rapid GS involves sequencing of the genome typically in less than 72 hours and is currently considered investigational.

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.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Standard Exome Sequencing	Genomic Unity Exome Plus Analysis - Proband (Variantyx)	0214U	F70-F79, F80.0-F89, Q00.0-Q99.9	1, 3, 5, 7, 9, 14
	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)			
Reanalysis of Whole Exome Sequencing Data	Exome Reanalysis (Ambry)	81417	F70-F79, F80-F89, Q00.0-Q99.9	4, 10, 12
Rapid Exome Sequencing	XomeDxXpress (GeneDx)	81415, 81416	F70-F79, F80-F89, Q00.0-Q99.9	2, 6, 7, 14
	ExomeNext-Rapid (Ambry)			
	PGxome RAPID Exome Test (PreventionGenetics, part of Exact Sciences)			
	STAT Whole Exome Sequencing (PerkinElmer Genomics)			
Standard Genome	Genomic Unity Whole Genome	0212U	F70-F79, F80-	7, 8,

Sequencing	Analysis - Proband (Variantyx Inc.)		F89, Q00.0-Q99.9	9, 11, 13, 14
	Genomic Unity® Whole Genome Analysis - Comparator (Variantyx 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		
	Praxis Combined Whole Genome Sequencing and Optical Genome Mapping (Praxis Genomics LLC)	0267U		
Rapid Genome Sequencing	Rapid Whole Genome Sequencing (Rady Children's Institute for Genomic Medicine)	0094U	F70-F79, F80-F89, Q00.0-Q99.9	2, 14
	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 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 meets one of the following:

      1. The member has unexplained epilepsy diagnosed at any age, **OR**
      2. The member has developmental delay or intellectual disability with onset prior to age 18 years, **OR**
      3. The member was diagnosed with one or more congenital anomalies before the age of 1 year, **OR**
      4. The etiology of the member's features is most likely genetic, based on **EITHER** of the following:

a) Multiple congenital abnormalities affecting unrelated organ systems, **OR**

b) **TWO** of the following:

(1) Abnormality of at least one 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. The member has not previously had whole 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. A diagnosis cannot be made in a timely manner by standard clinical evaluation, excluding invasive procedures such as muscle biopsy, **AND**

F. There is a predicted impact on the health outcome, including impact on medical management based on the results, **AND**

G. Pre- and post-test counseling by an appropriate provider, such as a Medical Geneticist, Genetic Counselor, or an Advanced Practice Nurse in Genetics (APGN), **AND**

H. The member and member's family history have been evaluated by a Medical Geneticist, Genetic counselor or an Advanced Practice Nurse in Genetics (APGN).

II. Repeat standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **not medically necessary**.

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 WHOLE EXOME SEQUENCING DATA

I. Reanalysis of whole exome sequencing data (81417) is considered **medically necessary** when*:

   A. The member previously had whole exome sequencing at least 18 months ago, **AND**

   B. The results of prior whole exome sequencing were non-diagnostic.

II. Reanalysis of whole exome sequencing data (81417) is considered **not medically necessary** for all other indications.

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

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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 member and member's family history have been evaluated by a Medical Geneticist, Genetic Counselor, or an Advanced Practice Nurse in Genetics (APGN), **AND**

   C. Non-genetic etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

D. 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:

        a) Abnormality affecting at least one organ system, **OR**

        b) Dysmorphic features, **OR**

        c) Encephalopathy, **OR**

        d) Symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia), **OR**

        e) Family history strongly suggestive of a genetic etiology, including consanguinity, **OR**

        f) Clinical or laboratory findings suggestive of an inborn error of metabolism, **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 clinical evaluation and other standard laboratory tests/imaging, etc., 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 Medical Geneticist, a Genetic Counselor, or an Advanced Practice Nurse in Genetics (APGN), **AND**

I. The member does **not** have any of the following:

    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.

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STANDARD GENOME SEQUENCING

I. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U, 0267U) is considered **medically necessary** when:

A. The member previously had uninformative whole exome sequencing (WES), **AND**

1. WES reanalysis is not possible, **OR**

B. The member meets at least one of the following:

1. The member has unexplained epilepsy diagnosed at any age, **OR**
2. The member has developmental delay or intellectual disability with onset prior to age 18 years, **OR**
3. The member was diagnosed with one or more congenital anomalies before the age of 1 year, **OR**
4. The etiology of the member's features is most likely genetic, based on **EITHER** of the following:

a) Multiple congenital abnormalities affecting unrelated organ systems, **OR**

b) **TWO** of the following criteria are met:

(1) Abnormality of at least one 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**

5. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

6. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted multi-gene panel testing is available, **AND**

7. There is a predicted impact on the health outcome, including impact on medical management based on the results, **AND**

8. Pre- and post-test counseling and evaluation by an appropriate provider, such as a Medical Geneticist, Genetic counselor or an Advanced Practice Nurse in Genetics (APGN)

C. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U, 0267U) is considered investigational for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

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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 member and member's family history have been evaluated by a Medical Geneticist, Genetic Counselor or an Advanced Practice Nurse in Genetics (APGN) **AND**

C. 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:

    1. Multiple congenital abnormalities affecting unrelated organ systems, **OR**

    2. **TWO** of the following:

        a) Abnormality affecting at least one 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 Medical Geneticist, Genetic Counselor, or an Advanced Practice Nurse in Genetics (APGN), **AND**

J. The member does **not** have any of the following:

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.

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NOTES AND DEFINITIONS

1. **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).
2. **Genome Sequencing (GS)** is a genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.
3. **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.
4. **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.

5. **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.
6. **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
7. **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.

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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)
- 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)

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)

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."

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:
    - 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

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)

Reanalysis of Whole Exome 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)

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)

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.

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)

Additionally, 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)

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)

Standard Genome Sequencing

American College of Medical Genetics and Genomics (ACMG)

A 2021 revision, published by Rehder, et al, 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/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. The potential impact of secondary findings with Exome Sequencing/Genome Sequencing should also be considered (section E.3).” (p. 1400-1401)

Abul-Husn et al.

In this study, performed in 2023, there were twice as many diagnoses in pediatric patients using whole genome sequencing (WGS) compared to targeted gene panel testing. The group concluded that genome sequencing may yield up to twice as many diagnoses in pediatric patients compared to targeted gene panel testing, but not yet across all population groups.

Chung, et al

A meta-analysis from 2023 compared the diagnostic and clinical utility of whole-exome sequencing (WES) versus whole-genome sequencing (WGS) in an ethnically diverse population of children and adults with rare disease. Results showed a similar diagnostic rate, although the odds of diagnosis by WGS was 1.2 times greater than WES. (p. 11) Meta-analysis of WES and WGS groups demonstrated that the pooled clinical utility of WGS (0.61) was higher than WES (0.48). (p. 13) The rate of variants of unknown significance (VUS) by WES and WGS did not differ significantly. (p. 15)

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

*Of note, the following guidelines were used for whole genome sequencing (WGS) test recommendations. Although they are focused on whole exome sequencing, it is the position of Concert Genetics that the recommendations could be extrapolated to WGS, as there are currently no specific guidelines for the use of this testing.

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:
  - 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

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.

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)

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.

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)

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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