Rapid Exome Sequencing

I. Rapid exome sequencing (rES), 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 multigene 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 criteria:

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 (rES) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

RATIONALE AND REFERENCES

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), which included the following:

- "We strongly recommend ES and GS as a first- or second-tier test… for patients with one or more congenital anomalies prior to one year of age, or for patients with intellectual disability/developmental delay with onset prior to 18 years of age (p. 2031).
- "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).

Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(11):2029-2037. doi:10.1038/s41436-021-01242-6

In 2020, ACMG released a systematic evidence-based review, which “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).

Malinowski J, Miller DT, Demmer L, et al. Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability. Genet Med. 2020;22(6):986-1004. doi:10.1038/s41436-020-0771-z

In 2022, ACMG released a clinical practice resource for the clinical evaluation of hearing loss, which 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).

Li MM, Tayoun AA, DiStefano M, et al. Clinical evaluation and etiologic diagnosis of hearing loss: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022;24(7):1392-1406. doi:10.1016/j.gim.2022.03.018

National Society for Genetic Counselors (NSGC)

The National Society for Genetic Counselors (NSGC) released a position statement (2013, updated 2020, reaffirmed 2023) 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.

Secondary and Incidental Findings in Genetic Testing. Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/secondary-and-incidental-findings-in-genetic-testing-1. Released September 27, 2013. Updated March 23, 2020. Reaffirmed 2023.

The National Society of Genetic Counselors (NSGC) published evidence-based practice guidelines for individuals with unexplained epilepsy (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.

Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2023;32(2):266-280. doi:10.1002/jgc4.1646

Patient-Centered Laboratory Utilization Guidance Services (PLUGS)

PLUGS released a guideline entitled “Genomic Sequencing for Rare Disease” in July of 2023. This guideline affirmed the medical necessity of exome sequencing when “(c)linical presentation does not fit a well-described syndrome for which more targeted testing is available,” the etiology remains unknown following clinical and radiological evaluation, and one of the following is true (p. 7):

- Specific features including epilepsy, bilateral sensorineural hearing loss, moderate to severe intellectual disability, global developmental delay, or multiple congenital anomalies are present

  OR

- A combination of personal and family history features including neuropsychiatric, metabolic, and single organ system abnormalities is present.

The guideline also includes a recommendation to rule out alternate etiologies prior to testing, when possible.

Genomic Sequencing for Rare Disease. Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services.
https://www.schplugs.org/wp-content/uploads/Genomic-Sequencing-in-Rare-Disease_2023_FINAL.pdf.
Effective July 2023.

Rehm, et al.

A 2023 paper by Rehm, et al. demonstrated that exome and genome sequencing had a significantly lower VUS rate (22.5%) compared to multigene panels (32.6%) (p. 5 and 6).

Rehm HL, Alaimo JT, Aradhya S, et al. The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change. Genet Med. 2023 Dec;25(12):100947. Epub 2023 Jul 30. doi:10.1016/j.gim.2023.100947.

Kingsmore, et al.

The NSIGHT2 study, a prospective randomized, controlled, blinded trial (RCT) in acutely ill infants, 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).

Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. Am J Hum Genet. 2019;105(4):719-733. doi:10.1016/j.ajhg.2019.08.009

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).

Bélanger SA, Caron J. Evaluation of the child with global developmental delay and intellectual disability. Paediatr Child Health. 2018;23(6):403-419. doi:10.1093/pch/pxy093

DEFINITIONS

1. **Autism spectrum disorder** is defined in the DSM V as persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:

    a. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

    b. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.

    c. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

2. **Close relatives** include first, second, and third-degree blood relatives:

    a. **First-degree relatives** are parents, siblings, and children

   b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

   c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

3. **Congenital anomalies** (according to ACMG) are anomalies not specific to a well-delineated genetic syndrome. These are structural or functional abnormalities requiring medical intervention that are usually evident at birth, or shortly thereafter, and are consequential to an individual's life expectancy, health status, or physical/social functioning.

4. **Developmental delay** (DD) is defined as 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.

5. **Dissection** refers to a tear in the inner layer of a main artery (aorta).

   a. **Type A aortic dissections** occur at the ascending part of the aorta, just as it branches off of the heart.

   b. **Type B aortic dissections** occur at the descending part of the aorta, and may extend into the abdomen.

6. **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).

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

8. **Global developmental delay** is diagnosed when a child under age 5 is slow-to-meet or not reaching milestones in the expected way for their age in at least two areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills). Examples include (but are not limited to): not sitting independently by 9 months; not crawling or rolling over by a year; not walking by 18 months (based on CDC Developmental milestones).

9. **Intellectual disability (ID)** is defined by the DSM V as an individual age 5 or older with either an IQ score of 70 or below, OR with a clinical diagnosis of intellectual disability per the DSM V, which includes all of the following:

    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.

10. **Mitochondrial disorder** refers to a heterogenous group of disorders caused by dysfunctional mitochondria, the organelles responsible for oxidative phosphorylation within the cell.

11. **Reanalysis of exome sequencing (ES) (aka exome sequencing reanalysis) or genome sequencing (GS) (aka genome sequencing reanalysis)** involves a bioinformatic re-review of both reported and unreported variants detected by the original assay. This is typically performed when (1) the patient's phenotype has changed and the changes are not explainable by the original result or (2) the original test was not diagnostic and the clinician or laboratory suspect that advances in variant classification or analysis pipelines may result in a diagnosis. Reanalysis may not be possible or useful in some situations due to changes in bioinformatic pipeline compatibility or new information regarding the genetic etiology of a condition that could explain the patient's clinical features but would not have been captured by previous ES or GS sequencing methods. **Exome sequencing reanalysis** or **Reanalysis of exome** 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.

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