Rapid Genome Sequencing

I. Rapid genome sequencing (rGS), 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 unexplained epilepsy, **OR**

      2. The member has multiple congenital abnormalities (functional and/or structural) affecting unrelated organ systems, **OR**

      3. The member has epileptic encephalopathy, **OR**

      4. 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) 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.

RATIONALE AND REFERENCES

Rapid Genome Sequencing

Patient-Centered Laboratory Utilization Guidance Services (PLUGS)

PLUGS released a guideline entitled “Rapid Genome Sequencing” in June of 2022. The authors specify that rapid genome sequencing (rGS) should be used only when (it) “is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis...” (p. 3 and 4).

This guideline affirmed the medical necessity of exome sequencing in “acutely-ill individuals” when their phenotype has an unknown, likely genetic etiology and one of the following is true:

- The patient has multiple multisystemic congenital anomalies or epileptic encephalopathy.
- A combination of personal and family history features including complex neurological conditions, single organ system or metabolic abnormalities, failure of standard treatment, or consanguinity present.
- Alternate etiologies have been considered and ruled out when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity).

Rapid Genome Sequencing. Seattle Children's Hospital Patient-centered Laboratory Utilization Guidance Services. https://www.schplugs.org/wp-content/uploads/Rapid-Genome-Sequencing-Policy_June-2022-FINAL.pdf Effective June 2022.

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

Kingsmore, et al.

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), compared 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).

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

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.

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.