Reanalysis of Exome or Genome Sequencing Data

I. Reanalysis of exome or genome sequencing data is considered **medically necessary** when[1]:

   A. The member had exome or genome sequencing at least 1 year ago, **OR**

   B. The member's phenotype has expanded to include clinical findings[2] 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 is considered **investigational** for all other indications.

[1]If reanalysis of exome data is not possible, see the genome sequencing criteria for additional coverage information.

[2]See Standard Exome Sequencing or Standard Genome Sequencing criteria for qualifying clinical findings.

RATIONALE AND REFERENCES

Reanalysis of Exome or Genome Sequencing Data

American Academy of Pediatrics (AAP)

This 2025 AAP report provided general guidance regarding genetic testing recommendations for individuals with global developmental delay (GDD) or intellectual disability (ID). The AAP took into consideration the diagnostic yield, cost of testing, and test complexity (p. 4) and proposed a "tiered agnostic approach" to diagnostic evaluation of GDD/ID (p. 5). In this approach, the Tier 1 testing includes exome or genome sequencing; Tier 2 testing includes Fragile X and inborn errors of metabolism, and Tier 3 includes genome sequencing (if not already performed), as well as additional more

specialized tests. They state that if Tier 3 testing is negative/uninformative, then exome or genome sequencing could be reanalyzed every 1-2 years following the initial test (p. 7).

Rodan LH, Stoler J, Chen E, Geleske T; Council on Genetics. Genetic evaluation of the child with intellectual disability or global developmental delay: clinical report. Pediatrics. 2025;156(1):e2025072219. doi:10.1542/peds.2025-072219

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).

Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. *Genet Med*. 2018;20(11):1328-1333. doi:10.1038/gim.2018.41

American College of Medical Genetics (ACMG)

A statement from ACMG (2019, reaffirmed 2023) included considerations for case-level exome reanalysis, 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).

Deignan JL, Chung WK, Kearney HM, et al. Points to consider in the reevaluation and reanalysis of genomic test results: a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21(6):1267-1270. doi:10.1038/s41436-019-0478-1

Reddi HV, Avenarius MR, Bean LJH, et al. Addendum: Points to consider in the reevaluation and reanalysis of genomic test results: A statement of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine. 2024;26(5):101100. doi:10.1016/j.gim.2024.101100

Patient-Centered Laboratory Utilization Guidance Services (PLUGS)

The PLUGS guidelines entitled “Genomic Sequencing for Rare Disease” (2023) 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).

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.

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.