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.

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. **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.

5. **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

6. **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.

REFERENCES

1. 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
2. "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.

3. 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) [published online ahead of print, 2021 Jul 1]. Genet Med. 2021;10.1038/s41436-021-01242-6. doi:10.1038/s41436-021-01242-6
4. “Exome Sequencing”. Seattle Children’s Hospital Patient-centered Laboratory Utilization Guidance Services. Whole Exome Sequencing_IBC (schplugs.org) October 2019.
5. Smith L, Malinowski J, Ceulemans S, Peck K, Walton N, Sheidley BR, Lippa N. Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. J Genet Couns. 2022 Oct 24. doi: 10.1002/jgc4.1646. Epub ahead of print. PMID: 36281494.
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. Published online July 30, 2023:100947.