Standard Exome Sequencing

I. Standard exome sequencing, with trio testing when possible, is considered **medically necessary** when:

A. The member has not previously had genome sequencing, **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 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 diagnosed at any age, **OR**

2. The member has global developmental delay or intellectual disability with onset prior to age 18 years, **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, epilepsy, 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) Autism, **OR**

f) Severe neuropsychiatric condition (e.g., schizophrenia, bipolar disorder, Tourette syndrome, self-injurious behavior, reverse sleep-wake cycles), **OR**

g) Period of unexplained developmental regression (unrelated to epilepsy or autism).

II. Repeat standard exome sequencing is considered **investigational**.

III. Standard exome sequencing is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

DEFINITIONS

1. **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.
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. **Intellectual disability** (ID) is defined by the DSM V as an individual with 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.

4. **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.

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