REANALYSIS OF EXOME OR GENOME SEQUENCING DATA

I. Reanalysis of exome or genome sequencing data (81417, 81427) is considered **medically necessary** when*:

   A. The member had exome or genome sequencing at least 18 months ago, **OR**

   B. The member's phenotype has expanded to include clinical findings** 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 (81417, 81427) is considered **investigational** for all other indications.

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

**See Standard Exome Sequencing or Standard Genome Sequencing criteria for qualifying clinical findings.

STANDARD GENOME SEQUENCING

I. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U), with trio testing when possible, is considered **medically necessary** when:

   A. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), **AND**

   B. Clinical presentation does not fit a well-described syndrome for which single-gene or targeted multi-gene panel testing is available, **AND**

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C. 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**

D. The member meets at least one of the following clinical findings:

1. The member previously had uninformative exome sequencing (ES), **AND**

    a) ES reanalysis is not possible, **OR**

2. The member has unexplained epilepsy diagnosed at any age, **OR**

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

4. The member was diagnosed with at least one congenital anomaly (functional and/or structural), **OR**

5. 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).

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II. Repeat standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) is considered **investigational**.

III. Standard genome sequencing (81425, 81426, 0212U, 0213U, 0265U) 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.

STANDARD EXOME SEQUENCING

I. Standard exome sequencing (81415, 81416, 0214U, 0215U), 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**

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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 (81415, 81416, 0214U, 0215U) is considered **investigational**.

III. Standard exome sequencing (81415, 81416, 0214U, 0215U) is considered **investigational** for all other indications, including screening asymptomatic/healthy individuals for genetic disorders.

DEFINITIONS

1. **Exome Sequencing (ES)**: 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)**: A genomic technique for sequencing the complete DNA sequence, which includes protein coding as well as non-coding DNA elements.

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

4. **Congenital anomalies:** According to ACMG, congenital anomalies 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. **Global Developmental delay:** An individual that is slow-to-meet or not reaching milestones in the expected way for a child's age in at least two of the areas of development (communication, gross/fine motor, cognition, social-emotional, or adaptive skills)

6. **Intellectual disability (ID):** Defined by the DSM-V as an individual who meets 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.

7. **Exome sequencing (ES) reanalysis** 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.

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