PRESBYTERIAN

Medical Policy

Subject: Genetic Testing for Whole Exome Sequencing (WES)

Medical Policy #: 7.12 **Original Effective Date: 05-25-2022**

Status: Reviewed **Last Review Date: 05-24-2023**

Disclaimer

Refer to the member's specific benefit plan and Schedule of Benefits to determine coverage. This may not be a benefit on all plans or the plan may have broader or more limited benefits than those listed in this Medical Policy.

Description

Genes are instructions for making proteins. These instructions are comprised of long strings of nucleotides - adenine (A), thymine (T), cytosine (C), and guanine (G) - which make up the human genome. Like letters that come together to correctly spell words, the precise order of these 4 nucleotides determines which proteins are made, and whether they are made correctly.

The genome is the entire string of nucleotides that a person has (approximately 3 billion), however not all the genome codes for proteins. The part of the human genome that codes for proteins is called the exome. It is errors (also called mutations) in the exome that cause most genetic disease. Whole exome sequencing (WES) uses Next Generation Sequencing technology to detect mutations in the exomes such as nucleotide substitutions, or large duplications or deletions.

Because WES evaluates all exomes at the same time, one challenge with WES is the enormous amount of information that is provided, which takes a geneticist or genetic counselor to interpret. For example, WES often discloses variants of unknown significance, and this information needs to be communicated with patients in appropriate language to ensure understanding and not cause undue anxiety. Or, there can be unexpected findings with potential medical importance (The American College of Medical Genetics recommends that over 70 genes be looked at for mutations regardless of why WES is being obtained, Miller 2021). An additional challenge with WES is that over time, as more is discovered about which mutations cause disease and which do not, old variants of unknown significance may become interpretable. Therefore it may be necessary to re-interpret WES data periodically, to determine whether prior variants of unknown significance are now known to be benign or pathologic.

Coverage Determination

Prior Authorization is required. Logon to Pres Online to submit a request: https://ds.phs.org/preslogin/index.jsp

For Medicare, Medicaid and Commercial.

Coverage Indications:

I. Medical Criteria

PHP considers WES medically necessary when *any* of the following criteria listed below are met in a child **<**18 years of age:

A. Multiple congenital anomalies
   a. Involving 2 or more organ systems

B. Ongoing developmental regression
   a. Unexplained, persistent loss of developmental milestones

C. Intellectual *or* developmental disability
   a. Intellectual disability
      1. Impaired intellectual function, > 2 standard deviations below mean on standard cognitive assessment, *and*
      2. Impaired adaptive function
   b. Developmental disability
      1. Impaired intellectual *or* physical function impacting adaptive skills

D. Medically refractory epilepsy
   a. Infantile epilepsy
      1. Individual < 3 years old
      2. Failed 2 antiseizure treatments
      3. Not explained by other etiologies (for example: acquired brain injury secondary to trauma, stroke, infection, environmental exposures)
   b. Pre-surgical workup
      1. Provider documents how results of WES affect surgical decision-making

II. Provider Criteria

PHP requires the following of the requesting provider:

A. WES is requested by board-certified geneticist **or** child neurologist.
B. Genetic counseling occurs before and after obtaining WES – this is provided by board-certified geneticist **or** genetic counselor.

III. Reanalysis of previously obtained uninformative whole exome or whole genome sequence data is considered medically necessary when the above criteria for whole exome/genome sequencing and ANY of the following conditions are met:

- Individual experiences additional symptoms after initial WES that cannot be explained by the results of the initial WES;

  or
- New data or new family history emerges which suggest a link between the individual's symptoms and specific genes

IV. Documentation Criteria

Submitted clinical documentation identifies:

A. How WES will affect patient management
B. Rationale for requesting WES instead of single gene test or targeted gene panel
C. Specialist consultation including examination findings and family pedigree
D. Pre-WES genetic counseling report includes at a minimum:
   a. Approach to variants of unknown significance
   b. Plan for addressing ACMG actionable genes
   c. Discussion of potential effect of results on other family members

V. **Exclusion**:

Due to insufficient evidence of efficacy, WES is unproven and not Medically Necessary for all other indications, including but not limited to the following:

- Evaluation of fetal demise
- Molecular profiling of tumors for the diagnosis, prognosis or management of cancer
- Preimplantation Genetic Testing (PGT) in embryos
- Prenatal genetic diagnosis or screening
- Screening and evaluating disorders in individuals when the above criteria are not met

Coding

The coding listed in this medical policy is for reference only. Covered and non-covered codes are within this list.

CPT®* Codes	Description
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure) (e.g. when both biological parents are to be tested then 81416 x2)
81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); **re-evaluation** of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family
HCPCS Code	**HCPCS Codes Description**
S0265	Genetic counseling, under physician supervision, each 15 minutes

Reviewed by / Approval Signatures

Clinical Quality & Utilization Mgmt. Committee: Gray Clarke MD
Senior Medical Director: David Yu MD
Medical Director: Ana Maria Rael
Date Approved: May 24, 2023

References

1. American College of Medical Genetics and Genomics (ACMG) Practice Guidelines, 2021, Published: 01 July 2021.

Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the ACMG, Kandamurugu Manickam. [Cited 03-07-2023]
2. Genetics inMedicine, Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders, Correction to: *Genetics in Medicine* **21**:2019; https://doi.org/10.1038/s41436-019-0554-6, published online 11 June 2019 [Cited 03/07/2023]
3. Genetic inMedicine, A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders, Issue Date: November 2016, Published: 03 March 2016. [Cited 03/07/2023]
4. United Healthcare, Whole Exome and Whole Genome Sequencing, Policy Number: 2023T0589M, Effective Date: March 1, 2023. [Cited 03-07-2023]
5. Aetna, Genetic Testing, Last Review 04-23-2021 Next Review: 02-10-2022, Number 0140. [Cited 03-07-2023]
6. BCBS of California, Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders, Original Policy Date: January 30, 2015, Effective Date: May 1, 2021. [Cited 03-07-2023]
7. Cigna, Whole Exome and Whole Genome Sequencing, Next Review Date: 01/15/2024, Policy Number: 0519. [Cited 03-07-2023]

Publication History

05-25-22	New policy. Whole Exome Sequencing was reviewed by TAC on October 19, 2021 and Jan 11, 2022. Reviewed by Medical Policy Committee on 05-11-2022. For Medicare, Medicaid and Commercial. The criteria are comparable with other payors regarding Medical criteria, Provider criteria and Documentation criteria. Continue prior authorization for 81415, 81416 and 81417. Pending review for preferred in-network labs.
05-24-23	Annual review. Reviewed by Medical Policy Committee on 03-08-2023. No change to main criteria. Two additional sections were added to policy. Added the section for *Reanalysis* with supporting criteria; and a section under *Exclusion*. No change to PA requirement. Format correction: changed the numbering format in section (II and IV).

This Medical Policy is intended to represent clinical guidelines describing medical appropriateness and is developed to assist Presbyterian Health Plan and Presbyterian Insurance Company, Inc. (Presbyterian) Health Services staff and Presbyterian medical directors in determination of coverage. The Medical Policy is not a treatment guide and should not be used as such.

For those instances where a member does not meet the criteria described in these guidelines, additional information supporting medical necessity is welcome and may be utilized by the medical director in reviewing the case. Please note that all Presbyterian Medical Policies are available online at: ***Click here for Medical Policies***

Web links:

At any time during your visit to this policy and find the source material web links has been updated, retired or superseded, PHP is not responsible for the continued viability of websites listed in this policy.

When PHP follows a particular guideline such as LCDs, NCDs, MCG, NCCN etc., for the purposes of determining coverage; it is expected providers maintain or have access to appropriate documentation when requested to support coverage. See the References section to view the source materials used to develop this resource document.