PRESBYTERIAN

Medical Policy

Subject: Genetic Testing for Whole Exome Sequencing (WES)

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

Status: Reviewed **Last Annual Review Date: 05-28-2025**

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 most of our proteins is called the exome. It is errors (also called mutations) in the exome that cause most genetic diseases. 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.

Additional Policies for Genomic Testing:

For Whole Genomic Sequencing, see Presbyterian **Laboratory Benefit Management (LBM) Policies: Policy Number: AHS – G2063 – Testing for Diagnosis of Active or Latent Tuberculosis**

See also MPM 7.1 Genetic and Genomic Testing

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

1. PHP considers WES medically necessary if you have been diagnosed before the age of 21 with *any* of the following list below:
   - 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. Epilepsy (e.g., intractable, early onset or epileptic encephalopathy)

2. Fetal testing for prenatal diagnosis via amniocentesis, chorionic villus sampling (CVS), or percutaneous umbilical blood sampling (PUBS), using exome sequencing is considered medically necessary when all of the following criteria are met:
   A. The fetus is affected with non-immune hydrops fetalis; and
   B. The member's current pregnancy has had a karyotype and/or microarray performed and the results were uninformative; and
   C. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, maternal condition).

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 **or** child neurologist.

III. Reanalysis of previously obtained uninformative whole exome sequence data is considered medically necessary when the above criteria for whole exome 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. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection)
C. Rationale for requesting WES instead of single gene test or targeted gene panel
D. Specialist consultation including examination findings and family pedigree
E. 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
- All other indications for fetal exome testing are considered experimental, investigational, or unproven for evaluation of a fetus during pregnancy or a terminated fetus.

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

Population Health & Clinical Quality Committee (PHCQC): Clinton White, MD

Senior Medical Director: Jim Romero, MD

Medical Director: Kresta Antillon, MD

Date Approved: May 28, 2025

Reviewed by:

- John Phillips MD, Neurologist, review date: 05/28/2025
- Mike Marble, MD. Professor of Pediatrics and Director of UNM Genetics, review date: 06-03-2024

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. *Accessed 5/1/2025*
2. **United Healthcare, Whole Exome and Whole Genome Sequencing,** Policy Number: 2024T0589Q Effective Date: April 01, 2024. [Cited 04/30/2024]
3. **Aetna, Genetic Testing,** Last Review 04-02/2025 Next Review: 02-16-2026, Number 0140. **[Cited 05/01/2025]**
4. 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 04/30/2024]
5. **Cigna, Whole Exome and Whole Genome Sequencing RETIRED**, Next Review Date: 01/15/2025, Policy Number: 0519. *Accessed 5/1/2025*
    a. *Cigna Evicore Adopted Policy:* ***Exome Sequencing****, MOL.TS.235.C, V1.0.2025,* **[Cited 5/1/2025]**
    b. *Cigna Evicore Adopted Policy:* ***Genome Sequencing****, MOL.TS.306.C, V2.0.2025,* **[Cited 5/1/2025]**
6. **New Mexico Health Care Authority (HCA) Letter of Direction (LOD) #42, Biomarker Coverage**, dated December 20, 2024 **[Cited 5/1/2025]**

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).
05-22-24	Annual review. Reviewed by Medical Policy Committee on 05/01/2024. Continue using the homegrown criteria with update on the language about the age. The criteria language about age changed from "PHP considers WES medically necessary when any of the following criteria listed below are met in a child <18 years of age" to say, "PHP considers WES medically necessary if you have been diagnosed before the age of 18 with any of the following list below."
05-28-25	Annual review. Reviewed by Medical Policy Committee on 5/14/2025. Homegrown material has been updated to follow suggested expansions comparable to other payers criteria that have become less restrictive. Less restrictive changes have been applied to allow for ages up to 21, and coverage criteria for Epilepsy (non-restrictive to type), as well as fetal testing coverage. Additional provider criteria added to II.B to allow for child neurologists for genetic counseling.

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.