Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS)

Policy Number: PG0468
Last Review: 04/01/2020

PARAMOUNT

ADVANTAGE | ELITE | HMO INDIVIDUAL MARKETPLACE | PROMEDICA MEDICARE PLAN | PPO

GUIDELINES

This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.

SCOPE

X Professional
X Facility

DESCRIPTION

Whole exome sequencing (WES) is a type of genetic testing that is used to determine the nucleotide sequence (or DNA sequence) of the exonic (the expressed or protein-coding) regions of an individual's genome. The exons represent approximately 1% of the complete DNA sequence (or genome). The exons contain the information that is used to make proteins required for normal growth, development and organ function. It is thought that about 85% of all mutations that cause genetic disease can be identified in the exons.

Whole genome sequencing (WGS) is another type of genetic testing, which seeks to determine an individual's entire DNA sequence (or genome). This testing examines both the exons (protein-coding regions) and introns (non-coding regions).

The American College of Medical Genetics and Genomics (2012) recommends that WGS/WES be considered in the "clinical diagnostic assessment of a phenotypically affected individual when:

a. The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis.
b. A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES or WGS analysis of multiple genes simultaneously a more practical approach.
c. A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
d. A fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis
    - Prenatal diagnosis by genomic (i.e., next-generation whole-exome or whole-genome) sequencing has significant limitations. The current technology does not support short turnaround times, which are often expected in the prenatal setting. There are high rates of false positives, false negatives, and variants of unknown clinical significance. These can be expected to be significantly higher than seen when array CGH is used in prenatal diagnosis."

In 2013, the American College of Medical Genetics and Genomics also published the following list of points to consider related to informed consent for ES (exome sequencing) and GS (genome sequencing):

1. "Before initiating GS/ES, counseling should be performed by a medical geneticist or an affiliated genetic counselor and should include written documentation of consent from the patient."

2. “Incidental/secondary findings revealed in either children or adults may have high clinical significance for which interventions exist to prevent or ameliorate disease severity. Patients should be informed of this possibility as a part of the informed consent process.”
3. “Pretest counseling should include a discussion of the expected outcomes of testing, the likelihood and type of incidental results that may be generated, and the types of results that will or will not be returned. Patients should know if and what type of incidental findings may be returned to their referring physician by the laboratory performing the test.”
4. “Patients should be counseled regarding the potential benefits and risks of GS/ES, the limitations of such testing, potential implications for family members, and alternatives to such testing.”
5. “GS/ES is not recommended before the legal age of majority except for:
    a. Phenotype-driven clinical diagnostic uses;
    b. Circumstances in which early monitoring or interventions are available and effective; or
    c. Institutional review board–approved research.”
6. “As part of the pretest counseling, a clear distinction should be made between clinical and research-based testing.”
7. “Patients should be informed as to whether individually identifiable results may be provided to databases, and they should be permitted to opt out of such disclosure.”
8. “Patients should be informed of policies regarding re-contact of referring physicians as new knowledge is gained about the significance of particular results.”

POLICY

HMO, PPO, Individual Marketplace, Advantage
Whole Exome Sequencing (WES) requires a prior authorization.

Elite/ProMedica Medicare Plan
Whole Exome Sequencing is non-covered.

HMO, PPO, Individual Marketplace, Elite/ProMedica Medicare Plan
Whole Genome Sequencing is non-covered.

Advantage
Whole Genome Sequencing (WGS) requires prior authorization.

COVERAGE CRITERIA

HMO, PPO, Individual Marketplace, Elite/ProMedica Medicare Plan, Advantage

Whole exome sequencing may be considered medically necessary if the results inform medical management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy or therapy that is more effective, avoid unnecessary therapy, or avoid unnecessary testing.

Whole Exome Sequencing (WES)
Whole exome sequencing may be considered medically necessary for the evaluation of unexplained congenital anomalies or neurodevelopmental disorders in children ≤21 years of age when ALL the following criteria are met:

- Diagnosing or evaluating a genetic disorder when the results are expected to directly influence medical management and clinical outcomes and all of the following criteria are met:
    - Clinical presentation is nonspecific and does not fit a well-defined syndrome for which a specific or targeted gene test is available. If a specific genetic syndrome is suspected, a single gene or targeted gene panel should be performed prior to determining if WES is necessary; and
    - The patient has been evaluated by a clinician with expertise in clinical genetics and counseled about the potential risks of genetic testing. WES is ordered by:
        - a board-certified medical geneticist,
        - a neonatologist in consultation with an independent genetic counselor (i.e. not laboratory-employed),
        - a neurologist in consultation with an independent genetic counselor, or

    - a developmental and behavioral pediatrician in consultation with an independent genetic counselor; and
  - One of the following:
    - Clinical and/or family history strongly suggest a genetic cause for which a specific clinical diagnosis cannot be made with any clinically available targeted genetic tests; or
    - A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (eg, chromosomal microarray analysis, targeted single-gene testing, and/or multi-gene panel); or
    - Previous genetic testing has failed to yield a diagnosis, and the affected individual is faced with invasive procedures or testing as the next diagnostic step (eg, muscle biopsy)
- Comparator (e.g., parents or siblings) WES for evaluating a genetic disorder when the above criteria have been met and WES is performed concurrently or has been previously performed on the individual

Whole Exome Sequencing (WES) is considered investigational, due to insufficient evidence of efficacy, is unproven and not medically necessary for all other indications not listed above, including but not limited to the following;

- General population screening
- Preimplantation genetic diagnosis or screening
- Prenatal (fetal) diagnosis or screening
- Fetal demise
- Molecular profiling of tumors (somatic testing) for diagnosis, prognosis or management of cancer

Trio Testing - of the child and both parents (and other family members if necessary) can increase the chance of finding a definitive diagnosis and better interpretation of results. Trio testing (whole exome with two comparator exomes) is preferred whenever possible but should not delay testing of a critically ill patient when rapid testing is indicated. Testing of one available parent should be done if both are not immediately available and one or both parents can be done later if needed.

Whole Genome Sequencing (WGS) is unproven and not medically necessary for screening and evaluating any genetic disorder due to insufficient evidence of efficacy. Although WGS is considered experimental and investigational by Paramount Health Care, it is a covered Ohio Medicaid benefit; therefore, WGS may be covered for Advantage members with prior authorization.

CODING/BILLING INFORMATION

The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

CPT CODES	
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)
81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); reevaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis

REVISION HISTORY EXPLANATION

ORIGINAL DATE: 04/01/2020

12/08/2020: Medical Policy placed on the new Paramount Medical Policy Format.

REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services

Ohio Department of Medicaid
American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services
Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets
Industry Standard Review
Medical Specialty Societies
Hayes, Inc. Genetic Test Evaluation (GTE)
ACMG Board of Directors. Points to consider in the clinical application of whole genome sequencing. Genetics in Medicine. 2012; 14:759–761.
ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. Genetics in Medicine. Sept 2013;15(9):748–749.