Whole Genome/Exome Sequencing and Genome-Wide Association Studies

Humana®

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Medical Coverage Policy

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Related Medical/Pharmacy Coverage Policies

Whole Mitochondrial Genome Sequencing and Multigene Panels for Mitochondrial Disorders

Description

Whole genome sequencing (WGS) is a laboratory test utilized to determine the sequence (arrangement) of an individual's entire genome at a single time. WGS allows the identification of mutations in the genome without having to target a gene or chromosome region based upon an individual's personal or family history. WGS may also be referred to as full genome sequencing, complete genome sequencing or entire genome sequencing.

Exome sequencing, also referred to as whole exome sequencing (WES), is an alternative to WGS. It is a laboratory test used to determine the sequence of the protein coding regions of the genome. The exome is the part of the genome that encodes protein, where roughly 85% of variants are known to contribute to diseases in humans. Exome sequencing has been proposed as a diagnostic method to identify these genetic variants in an individual not diagnosed by traditional diagnostic and genetic testing approaches.
WES has been proposed as a methodology to analyze **tumor mutational burden (TMB)**, an emerging biomarker that measures the number of mutations (changes) within the deoxyribonucleic acid (DNA) of

cancer cells using tumor biopsy tissue. Determining TMB may be helpful for treatment decisions as well as assessing potential eligibility for clinical trials. An example of a WES test that measures TMB is Omics Core.

Another suggested use for WES is for the detection of **minimal residual disease (MRD)** which is a term used for hematologic malignancies and is defined as the small number of cancer cells that remain in the body following treatment. Examples include, but may not be limited to, Invitae PCM Tissue Profiling and MRD Baseline Assay and Invitae PCM MRD Monitoring.

Exome custom panels (also known as exome backbone tests) are customizable, next-generation sequencing (NGS) assays that utilize the whole exome sequencing platform to sequence single genes or multigene panels. Healthcare providers select genes from a menu of genes to include in the request. These tests, depending on the results, may also reflex to (automatically trigger further testing) exome sequencing. Examples include Custom Slice, Custom Slice Xpanded and Slice.

Duo and trio WES involves testing family members in addition to the proband (first affected individual in a family) to facilitate a diagnosis. Duo WES is performed in the proband and one biologically related individual, typically a parent or sibling. Trio WES is performed using samples from the proband and two relatives, typically both parents. The evaluation of the relatives is referred to as comparator analysis.

A **genome-wide association study (GWAS)**, also referred to as genome-wide analysis, is a method to identify genes involved in human disease by comparing the genome of an individual who have a disease or condition to the genome of an individual without the disease or condition. GWAS are performed using microarrays to search the genome for small variations, called single nucleotide polymorphisms (SNPs) that occur more often in an individual with a specific disorder than in those who do not have a disorder.

Optical genome mapping (OGM) is a technology used to enhance the detection and interpretation of WGS by analyzing ultra-high molecular weight DNA molecules that provides a high-resolution genome-wide analysis highlighting copy number and structural anomalies, including balanced translocations. Examples of OGM testing include, but may not be limited to:

- Augusta Hematology Optical Genome Mapping
- Augusta Optical Genome Mapping
- Chromosome Genome Mapping
- DH Optical Genome Mapping/Digital Karyotyping Assay
- Praxis Optical Genome Mapping
- Praxis Somatic Optical Genome Mapping

OGM may be offered in combination with WGS. Examples include, but may not be limited to:

- Praxis Combined Whole Genome Sequencing and Optical Genome Mapping
- Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping

WGS/WES reanalysis or reevaluation involves taking the raw data generated from a previous WGS/WES study and reprocessing it using updated software and new reference genome versions. Reanalysis or reevaluation differs from retesting.

Transcriptome sequencing is a method of analyzing the complete set of RNA molecules, or transcripts, produced by a cell or tissue at a specific time. Praxis Somatic Transcriptome and Praxis Transcriptome are examples of this type of testing.

Coverage Limitations

Any state mandates for WGS, WES or GWAS take precedence over this medical coverage policy.

Humana members may **NOT** be eligible under the Plan for **WGS, WES or GWAS** for any indication or test including, but may not be limited to:

- Carrier status or reproductive risk including, but may not be limited to:
    - Insight Genome
    - Repro Xpanded Test (individual or couple)
- Combined WES and mitochondrial genome testing including, but may not be limited to:
    - Comparator (parent, sibling) for rare disease (constitutional/heritable disorders) (eg, Genomic Unity Exome Plus Analysis – Comparator [0215U])
    - Proband (first affected individual in a family) for rare disease (constitutional/ heritable disorders) (eg, Genomic Unity Exome Plus Analysis – Proband [0214U])
    - XomeDx Plus Test
- Combined WGS and mitochrondrial genomic testing including, but may not be limited to:
    - Comparator (parent, sibling) for rare disease (constitutional/heritable disorders) (eg, Genomic Unity Whole Genome Analysis – Comparator [0213U])
    - Proband (first affected individual in a family) for rare disease (constitutional/heritable disorders) (eg, Genomic Unity Whole Genome Analysis – Proband [0212U])
- Combined WGS and OGM including, but may not be limited to:
    - Praxis Combined Whole Genome Sequencing and Optical Genome Mapping (0267U)
    - Praxis Somatic Combined Whole Genome Sequencing and Optical Genome Mapping (0300U)
- Custom exome panels of single or targeted genes (eg, Custom Slice, Custom SliceXpanded, Slice)
- Duo and Trio WGS or WES including, but may not be limited to:

  - XomeDx – Duo
  - XomeDx – Trio

- Evaluation of any of the following:

  - Alzheimer disease/dementia
  - Ataxia
  - Autism spectrum disorder
  - Congenital anomalies
  - Developmental delay/intellectual disability
  - Dystonia
  - Epilepsy
  - Hearing loss
  - Primary immunodeficiency
  - Psychiatric conditions
  - Stillbirth/fetal demise

- Fetal evaluation including, but may not be limited to, XomeDx Fetal, IriSight CNV Analysis (0469U)

- MRD assessment (baseline or monitoring) by WGS or WES including, but may not be limited to:

  - Invitae PCM Tissue Profiling & MRD Baseline Assay (0306U)
  - Invitae PCM MRD Monitoring (0307U)
  - Precise MRD

- OGM including, but may not be limited to:

  - Augusta Hematology Optical Genome Mapping (0331U)
  - Augusta Optical Genome Mapping (0260U)
  - Chromosome Genome Mapping (0454U)
  - DH Optical Genome Mapping/Digital Karyotyping Assay (0413U)
  - Praxis Optical Genome Mapping (0264U)
  - Praxis Somatic Optical Genome Mapping (0299U)

- Preimplantation genetic testing

- Prenatal screening or diagnosis by WGS or WES including, but may not be limited to:

  - ExomeNext Prenatal
  - IriSight Prenatal Analysis (comparator [0336U] or proband [0335U])
  - XomeDx Prenatal Test (comprehensive or targeted)
- Rapid or ultrarapid WGS or WES including, but may not be limited to:

  - Custom SliceXpanded Priority
  - Custom SliceXanded Xpress Test

  - GenomeXpress Test
  - NICUXpress Panel
  - RCIGM Rapid Whole Genome Sequencing [0094U])
  - RCIGM Rapid Whole Genome Sequencing, Comparator Genome (0425U)
  - RCIGM Ultra-Rapid Whole Genome Sequencing (0426U)
  - XomeDx Priority Test
  - XomeDxXpress Test

- Reanalysis or reevaluation by WGS or WES including, but may not be limited to:

  - Xome Reanalysis Test
  - Xome Subsequent Reanalysis Test

- Somatic WGS or WES including, but may not be limited to:

  - EXaCT-1 Whole Exome Testing [0036U])
  - Praxis Somatic Whole Genome Sequencing (0297U)
  - Tempus xE

- Targeted gene rearrangement detection by WGS NGS for any of the following:

  - Germline congenital disorders (eg, MatePair Targeted Rearrangements, Congenital [0012U])

  - Hematology (acute myelogenous leukemia [AML]) (eg, MatePair Acute Myeloid Leukemia Panel [0056U])

  - Hematology (hematolymphoid neoplasia) (eg, MatePair Targeted Rearrangements, Hematologic [0014U])

  - Oncology (solid organ neoplasia) (eg, MatePair Targeted Rearrangements, Oncology [0013U])

- TMB assessment by WGS or WES including, but may not be limited to, Omics Core whole exome tumor-normal in vitro diagnostic

- Transcriptome including, but may not be limited to:

  - Praxis Somatic Transcriptome (0298U)
  - Praxis Transcriptome (0266U)

- WGS including, but may not be limited to, Praxis Whole Genome Sequencing (0265U)

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	**Not Covered**
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)	**Not Covered**
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)	**Not Covered**
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis	**Not Covered**
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)	**Not Covered**
81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)	**Not Covered**
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses	**Not Covered**
0094U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis	**Not Covered**

0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	**Not Covered**
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)	**Not Covered**
0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	**Not Covered**
0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling)	**Not Covered**
0260U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping	**Not Covered**
0264U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping	**Not Covered**
0265U	Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffin-embedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants	**Not Covered**

0266U	Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes	**Not Covered**
0267U	Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing	**Not Covered**
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification	**Not Covered**
0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification	**Not Covered**
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification	**Not Covered**
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification	**Not Covered**
0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient specific panel for future comparisons to evaluate for MRD	**Not Covered**
0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD	**Not Covered**
0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alterations	**Not Covered**

0335U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants u(Do not report 0335U in conjunction with 81425, 0212U)t	**Not Covered**
0336U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent) u(Do not report 0336U in conjunction with 81426, 0213U)t	**Not Covered**
0413U	Oncology (hematolymphoid neoplasm), optical genome mapping for copy number alterations, aneuploidy, and balanced/complex structural rearrangements, DNA from blood or bone marrow, report of clinically significant alterations	**Not Covered** **New Code Effective 10/01/2023**
0425U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (eg, parents, siblings)	**Not Covered** **New Code Effective 01/01/2024**
0426U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis	**Not Covered** **New Code Effective 01/01/2024**
0454U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping	**Not Covered** **New Code Effective 07/01/2024**
0469U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of	**Not Covered** **New Code Effective 07/01/2024**

	genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

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Change Summary

07/01/2024 Provider Claims Codes Update, No Coverage Change.