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Whole Exome Sequencing, Whole Genome Sequencing, and Genome Wide Copy Number Variant Analysis

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Scope

This evidence-based guideline addresses the diagnostic use of whole genome copy number variant analysis (e.g., chromosomal microarray analysis [CMA] and low-pass whole genome sequencing), whole exome sequencing (WES), and whole genome sequencing (WGS) in the evaluation of rare disease. This guideline also addresses other broad scale profiling, e.g. whole transcriptome analysis and genome mapping.

This guideline's coverage criteria delineate medically necessary clinical scenarios for molecular testing and may include specific situations when testing is considered never medically necessary. In general, molecular testing is considered never medically necessary when evidence demonstrating its ability to improve diagnosis, management, or clinical outcomes is lacking in peer-reviewed literature.

- This guideline does not address the use of WES as a technology for tumor profiling or genome wide copy number variant analysis, e.g., chromosomal microarray analysis, for oncology indications (please refer to the Somatic Tumor Testing guideline).
- This guideline does not address the use of whole genome copy number variant analysis, e.g., chromosomal microarray analysis, for fetal indications (please refer to the Molecular Testing for Infertility and Pregnancy Loss or the Preimplantation Testing, Prenatal Cell-Free DNA Screening, and Prenatal Diagnosis guidelines).

State Biomarker Legislation

Medical necessity determinations must also take into consideration controlling state coverage mandates that may supersede these guidelines when applicable. When state biomarker legislation requirements impact coverage decisions, this guideline will initially be applied to determine if criteria are met for approval. If an approval cannot be granted based on the criteria in this guideline, some or all of the following sources will be reviewed, as defined by applicable state legislation, to determine if test coverage is supported in a manner that is consistent with the state biomarker legislation requirements:

- Medicare National Coverage Determinations (NCDs)
- Medicare Local Coverage Determinations (LCDs)
- U.S. Food and Drug Administration (FDA) approved or cleared tests
- Tests indicated for an FDA-approved drug
- Nationally recognized clinical practice guidelines
- Consensus statements

Guideline Coverage Criteria

General Criteria for Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS)

WES/WGS is medically necessary when all of the following criteria are met:

- Results will directly impact clinical decision-making and/or clinical outcome
- No other causative circumstances (e.g., environmental exposures, injury, prematurity, infection) can explain symptoms
- Clinical presentation does not fit a well-described syndrome for which single-gene or targeted panel testing is available
- The differential diagnosis list and/or phenotype warrant testing of multiple genes, and at least one of the following:
    - WES/WGS is more practical than the separate single gene tests or panels that would be recommended based on the differential diagnosis
    - WES/WGS results may preclude the need for multiple and/or invasive procedures, follow-up, or screening ("diagnostic odyssey") that would be recommended in the absence of testing

Phenotype Suspicious for a Genetic Diagnosis

WES (81415 with or without 81416) or WGS (81425 with or without 81426) are medically necessary when testing is ordered after an individual has been evaluated by a board-certified medical geneticist or other board-certified specialist physician with specific expertise in the conditions being tested for and relevant genes, general criteria for testing above are met, AND any of the following:

- Individual with multiple major structural or functional congenital anomalies affecting unrelated organ systems (including major metabolic disorders), **OR**
- Individual with one major structural or functional congenital anomaly and two or more minor structural anomalies, **OR**
- Individual with one major structural congenital anomaly and a family history strongly implicating a genetic etiology **OR**
- Individual with known or suspected developmental and epileptic encephalopathy (onset before three years of age) for which likely non-genetic causes of epilepsy (e.g., environmental exposures; brain injury secondary to complications of extreme prematurity, infection, trauma) have been excluded, **OR**
- Individual diagnosed with global developmental delay* following formal assessment by a developmental pediatrician or neurologist, **OR**
- Individual diagnosed with moderate/severe/profound intellectual disability** following formal assessment by a developmental pediatrician or neurologist, **OR**
- Individual with confirmed congenital bilateral sensorineural hearing loss of unknown etiology

*Global developmental delay is defined as significant delay in younger children, <5 years of age, in at least two of the major developmental domains: gross or fine motor; speech and language; cognition; social and personal development; and activities of daily living.

**Moderate/severe/profound intellectual disability as defined by DSM-5 criteria diagnosed by 18 years of age.

Fetal Testing

WES (81415 with or without 81416) is medically necessary when general criteria for testing above are met and all of the following criteria:

- Standard diagnostic genetic testing (chromosomal microarray analysis [CMA] and/or karyotype) of the fetus has been performed and is uninformative **AND**
- Testing is ordered in conjunction with a board-certified medical geneticist or genetic counselor **AND**
- Testing is performed on direct amniotic fluid/chorionic villi, cultured cells from amniotic fluid/chorionic villi, or DNA extracted from fetal blood or tissue **AND**
- At least one of the following is present:
    - Multiple fetal structural anomalies affecting unrelated organ systems
    - Fetal hydrops of unknown etiology
    - A fetal structural anomaly affecting a single organ system (please note exclusions below)
        - Isolated anomalies excluded from coverage:
            - Isolated increased nuchal translucency
            - Isolated talipes (clubfeet)
            - Isolated neural tube defect
            - Isolated cleft lip and/or palate
            - Isolated congenital diaphragmatic hernia

Fetal WES is not medically necessary for any of the following indications:

- Healthy pregnancies
- Indications other than fetal structural anomalies
- Ultrasound soft markers of aneuploidy (e.g., choroid plexus cysts, echogenic bowel, intracardiac echogenic focus)

Fetal testing with whole genome sequencing is not medically necessary.

WES/WGS is not medically necessary in the following scenarios:

- Testing using cell-free DNA
- Preimplantation testing of an embryo
- Genetic carrier screening
- Elective genomic testing (WES/WGS)

- Oncology indications
- Isolated mild intellectual disability
- Isolated autism spectrum disorder
- Whole genome sequencing of the transcriptome (RNA sequencing)
- Genome mapping

Whole Exome Reanalysis

Reanalysis of previously obtained uninformative whole exome sequence (81417) is medically necessary when any of the following criteria is met:

- There has been onset of additional symptoms that broadens the phenotype assessed during the original exome evaluation
- There has been the birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture
- New scientific knowledge suggests a previously unknown link between the patient's findings and specific genes/pathogenic or likely pathogenic variants AND at least 18 months have passed since the last analysis

Genome Wide Copy Number Variant Analysis

Genome wide copy number variant analysis (81228, 81229, 81349), using chromosomal microarray analysis or low-pass whole genome sequencing, is medically necessary in the following clinical scenarios.

- Biological parent of a fetus/child with an equivocal or a pathogenic/likely pathogenic copy number variant (CNV) result
- Individual with non-syndromic autism spectrum disorder
- Individual with non-syndromic global developmental delay or intellectual disability*
- Individual with one major anomaly and suspicion for a syndrome caused by a copy number variant, e.g. 22q11.2 deletion syndrome*
- Individual with multiple major structural or functional congenital anomalies affecting unrelated organ systems (including major metabolic disorders)*
- Individual with known or suspected developmental and epileptic encephalopathy (onset before three years of age) for which likely non-genetic causes of epilepsy (e.g. environmental exposures; brain injury secondary to complications of extreme prematurity, infection, trauma) have been excluded*

* *Copy number variant analysis is intended for use in the detection of chromosomal duplications and deletions only and is therefore indicated when the possibility of microdeletion or microduplication syndromes/conditions are suspected. It cannot detect other common variant types (e.g., sequence variants). If sequence variants are high on*

the differential diagnosis, please see the criteria above for whole exome and whole genome sequencing.

Key Terms and Definitions

Aneuploidy is characterized by an extra or missing chromosome, as seen in conditions such as Down syndrome (trisomy 21), trisomy 13, or trisomy 18.
Cell-free DNA refers to fragments of DNA that are released from damaged or dying cells and can be identified in bodily fluids like the blood.
Chromosomes carry genetic material known as DNA; humans typically have 23 pairs of chromosomes.
Chromosomal microarray analysis is a genetic test that analyzes the entire genome for small deletions or duplications, known as copy number variants, in the DNA.
Congenital anomaly refers to a structural or functional abnormality present in a baby at the time of birth which may result from genetic factors, environmental exposures during pregnancy, or a combination of both. Structural congenital anomalies involve physical malformations of body parts or organs. Functional congenital anomalies refer to an abnormality in the normal functioning of a specific organ or system and do not necessarily involve visible structural changes.
Copy number variants are small deletions or duplications in the DNA.
Deoxyribonucleic acid (DNA) is a molecule that contains the genetic instructions for all living organisms and plays a crucial role in the development and susceptibility to diseases.
Exome refers to all of the protein-coding regions in the genome; although it includes only 1-2% of the entire genome, it contains most disease-causing genes.
First-degree relative refers to a biological parent, sibling, or child.
Genes are segments of DNA that contain the instructions for specific traits, characteristics, or functions within an organism.
Genetic (molecular) testing examines a person's DNA or RNA to identify variations that can aid in the diagnosis of disease and/or provide valuable information about a person's risk of developing certain diseases.
Genome refers to an individual's entire set of genetic material (DNA).
Genome mapping involves identifying and sequencing all the genes, non-coding regions, and repetitive sequences that make up an individual's genetic material.
Genotype is the genetic makeup of an individual.
Low-pass whole genome sequencing is a cost-effective and efficient method of whole genome sequencing that involves using a lower coverage depth (the number of times each base pair in the genome is read during sequencing) compared to traditional whole genome sequencing.
Microdeletions refer to the loss of a small segment of DNA from one of the chromosomes.
Microduplications refer to the gain of a small segment of DNA from one of the chromosomes.
Non-syndromic refers to a medical condition or disorder that occurs without other associated clinical features or symptoms commonly seen in a specific group of disorders known as syndromes.
Pathogenic/likely pathogenic variant(s) are specific genetic changes that are known or highly likely to cause a particular genetic disorder, which can aid in diagnosis and/or guide treatment and management strategies.
Pharmacogenomics is a type of precision medicine that studies the influence of an individual's genotype on their body's response to medications.
Phenotype refers to the observable characteristics or features of a genetic disorder.
Preimplantation genetic testing (PGT) is a genetic test used to screen embryos created during in vitro fertilization (IVF) for specific genetic disorders or chromosomal abnormalities.
Sequence variant, also known as a genetic variant, refers to a specific change or alteration in the DNA

sequence when compared to a reference or normal sequence, which can have various effects on an individual's phenotype or health.
Whole exome sequencing (WES) is a technology that involves sequencing the entire exome.
Whole genome sequencing (WGS) is a technology that involves sequencing the entire genome.
Whole transcriptome analysis, also known as RNA sequencing, is a technology that analyzes the complete set of RNA molecules produced by a cell or organism.

CPT® Codes

Medical necessity review of claims may include evaluation of the submitted codes. Laboratories must accurately represent their services using the most applicable and specific CPT code(s). Tier 1 molecular pathology procedure codes or Proprietary Laboratory Analyses (PLA) codes should be used when available for the specific test. Tier 2 molecular pathology procedure codes should only be used if the American Medical Association (AMA) has specifically assigned the performed test to such a code. Genomic sequencing procedures (GSP) codes (e.g., CPT codes 81410-81471) were developed by the AMA to represent multi-gene panels utilizing DNA or RNA analysis for specific clinical scenarios (e.g., carrier screening, tumor testing, etc.) and should be utilized when applicable.

Coding guidelines can be found in the AMA's CPT manual as well as the Centers for Medicare and Medicaid Services (CMS) National Correct Coding Initiative (NCCI) policy manuals. NCCI General Correct Coding Policy states that procedures should be reported with the most comprehensive CPT code describing the services performed and that the services described by a CPT code cannot be unbundled into multiple less specific codes. Additionally, GSP codes should be utilized when appropriate for the described test and should not be submitted along with other CPT codes that represent components of the GSP code.

Claims may not be approved if the submitted codes are not the most appropriate for the described procedure (i.e., as accurate and specific as available).

The following code(s) are medically necessary when coverage criteria are met. This list is not all inclusive.

Code	Full Description
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
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)
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained

	exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
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)
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
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 (Do not report 0212U in conjunction with 81425)
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) (Do not report 0213U in conjunction with 81426)
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 (Do not report 0214U in conjunction with 81415)
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) (Do not report 0215U in conjunction with 81416)
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

The following code(s) are considered never medically necessary. This list is not all inclusive.

Code	Full Description
81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
0260U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
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
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
0454U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping

References

CPT Codes

AMA CPT® Professional 2024. American Medical Association

NCCI Policy Manual for Medicare Services. Available at: https://www.cms.gov/Medicare/Coding/NationalCorrectCodInitEd. Accessed quarterly.

NCCI Policy Manual for Medicaid Services. Available at: https://www.medicaid.gov/medicaid/program-integrity/national-correct-coding-initiative/medicaid-ncci reference-documents/index.html

Whole Exome Sequencing

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Change Summary

Version	Review Date	Effective Date	Summary of Revisions
Created	CSC: 8/11/2022 PAB: 9/12/2022	November 2022	Not applicable
v1.2023	COOC: 2/15/2023 PAB: 3/16/2023	April 1, 2023	Semi-annual review. No criteria changes.
v2.2023	COOC:8/16/2023 PAB: 9/25/2023	October 1, 2023	Semi-annual review. No criteria changes.
v1.2024	COOC: 2/14/2024 PAB: 3/25/2024	April 1, 2024	Semi-annual review. No criteria changes. Clarifications were made to the scope and CPT code sections. References were updated.
v2.2024	COOC:08/19/2024 PAB: 09/20/2024	October 1, 2024	Semi-annual review. Criteria for Fetal WES was expanded to no longer exclude isolated congenital heart defects. References were updated.
v1.2025	COOC: 02/17/2025 PAB: 03/24/2025	July 3, 2025	Semi-annual review. No criteria changes.