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Department of Origin: Integrated Healthcare Services	**Effective Date:** 03/21/24
Approved by: Medical Policy Quality Management Subcommittee	**Date Approved:** 06/06/23
Clinical Policy Document: Genetic Testing, Whole Exome and Whole Genome Sequencing	**Replaces Effective Clinical Policy Dated:** 06/06/23
Reference #: MC/L021	**Page:** 1 of 6

PURPOSE:
The intent of this clinical policy is to ensure services are medically necessary.

Please refer to the member's benefit document for specific information. To the extent there is any inconsistency between this policy and the terms of the member's benefit plan or certificate of coverage, the terms of the member's benefit plan document will govern.

POLICY:
Benefits must be available for health care services. Healthcare services must be ordered by a provider. Licensed Genetic Counselors may also order genetic tests if it is within the scope of practice of their state licensure. Healthcare services must be medically necessary, applicable conservative treatments must have been tried, and the most cost-effective alternative must be requested for coverage consideration.

GUIDELINES:
Medical Necessity Criteria - Requests for whole exome sequencing (WES) or whole genome sequencing (WGS) – Must satisfy all of the following: I - III, and one of IV-VI

I. A *health care professional trained in genetics*, independent of the laboratory performing the testing, has reviewed and documented family history, advised the member of the potential harms/benefits of the testing and implications of the test results, and obtained written formal consent; and

II. The result of the test will directly impact the current treatment being delivered to the member; and

III. After history, physical examination, and completion of conventional diagnostic studies (eg, karyotyping, muscle biopsy), a definitive diagnosis remains uncertain; and

IV. Member displays clinical features of a genetic disorder but gene-specific or targeted-sequencing tests available for that *phenotype* have failed to arrive at a diagnosis; or

V. Member displays clinical features of a genetic disorder but due to the high degree of genetic heterogeneity, gene specific or targeted-sequencing tests are not available; or

VI. Member displays clinical features that strongly implicate a genetic etiology but the *phenotype* does not correspond with a specific disorder, as evidenced by the following: A or B

   A. Multiple congenital abnormalities (CA) affecting unrelated organ systems; or

   B. Member has two or more of the following: 1 – 6

      1. Abnormality affecting at minimum a single organ system (eg, brain); or

      2. A formal diagnosis of autism, significant developmental delay (DD), or intellectual disability (ID) (eg, characterized by significant limitations in both intellectual functioning and in adaptive behavior); or

      3. Symptoms of a complex neurodevelopmental disorder (eg, self-injurious behavior, reverse sleep-wake cycles, dystonia, ataxia, alternating hemiplegia, neuromuscular disorder); or

4. Severe neuropsychiatric condition (eg, schizophrenia, bipolar disorder, Tourette syndrome); or

5. Period of unexplained developmental regression; or

6. Biochemical findings suggestive of an inborn error of metabolism.

[Note: Comparator family trio testing (81416, 0213U, 0215U) whole exome/genome sequencing of the biologic parent(s) or sibling of the affected member) can be allowed when criteria for whole exome/genome sequencing of the affected member are met]

NOT ROUTINELY COVERED
Re-evaluation of previously obtained exome or genome sequence (81417, 81427)

EXCLUSIONS (not limited to):
Refer to member's Certificate of Coverage or Summary Plan Description

Whole genome sequencing for all other indications is investigative (see Investigative List)

DEFINITIONS:
Analytic Validity:
How accurately and reliably the test measures the genotype of interest. A major component in the validation of an analytical technique is the technique's ability to accurately determine the presence of the substance it is seeking. It must measure the target substance without a great range of variation over a number of trials. The technique also must be proven to work reliably at multiple labs to be validated by this testing.

Clinical Utility:
The evidence of improved measurable clinical outcomes, and its usefulness and added value to patient management decision-making compared with current management without the testing.

Clinical Validity:
How consistently and accurately the test detects or predicts the intermediate or final outcomes of interest.

Health care professionals trained in genetics:
A genetics professional has experience and an educational background in genetics, counseling, and hereditary syndromes to provide accurate risk assessment and empathetic genetic counseling to patients and their families. Genetics professionals include people certified in any of the following ways:

- American Board of Genetic Counseling (ABGC) or American Board of Medical Genetics and Genomics (ABMGG) board certified/board eligible[15] or a licensed genetic counselor
- Advanced Genetics Nursing Certification (AGN-BC)[15]
- Advanced Clinical Genomics Nurse (ACGN) credential[15]
- Clinical Genomics Nurse (CGN) certification[15]
- Cancer Genetic Risk Assessment (CGRA) certification[15]

- Advanced practice oncology nurse or physician assistant with specialized education in cancer genetics and hereditary cancer predisposition syndromes[15]
- Board-certified/board-eligible physician with experience in cancer genetics (defined as education resulting in a certification and undergoing ongoing continuing medical education in cancer genetics and hereditary cancer predisposition syndromes)[15]
- A registered nurse with specialized education in cancer genetics and hereditary cancer predisposition syndromes (defined as education resulting in a certification and undergoing ongoing continuing medical education in cancer genetics and hereditary cancer predisposition syndromes)[15]
- Board-certified specialty care physician with experience in the diagnosis and treatment of the hereditary condition, eg, cardiologist ordering genetic testing for hypertrophic cardiomyopathy

Phenotype:
The physical expression, or characteristics, of a specific trait.

Regulatory/oversight body:
Such as, but not limited to, Clinical Laboratory

BACKGROUND:
The genome, or genetic material, of an organism (bacteria, virus, potato, human) is made up of DNA. Each organism has a unique DNA sequence which is composed of bases (A, T, C, and G). If you know the sequence of the bases in an organism, you have identified its unique DNA fingerprint, or pattern. Determining the order of bases is called sequencing. Whole genome sequencing is a laboratory procedure that determines the order of bases in the genome of an organism in one process.

The “exome” is the component of the genome that predominantly encodes protein; these segments are referred to as “exons” and can include noncoding exons. The exome comprises about 1% of the genome and is, so far, the component most likely to include interpretable mutations that result in clinical phenotypes. Whole exome sequencing involves determination of the DNA sequence of most of these protein-encoding exons and may include some DNA regions that encode RNA molecules that are not involved in protein synthesis.

Prior Authorization: Yes**,** per network provider agreement

CODING:
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)
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)
81427 Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genomic sequence (eg, updated knowledge or unrelated condition/syndrome
0094U Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
0209U Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
0212U Rare disease, (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
0213U Rare disease, (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)
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 categorizations of gene variants, proband
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 categorizations of gene variants, each comparator exome (eg, parent, sibling)
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
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
0425U Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (eg, parents, siblings)
0426U Genome (eg, unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis

REFERENCES:

1. Integrated Healthcare Services Process Manual: UR015 Use of Medical Policy and Criteria
2. Clinical Policy: MP/C009 Coverage Determination Guidelines
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Grievance Specialist
PreferredOne Community Health Plan
PO Box 59052
Minneapolis, MN 55459-0052
Phone: 1.800.940.5049 (TTY: 763.847.4013)
Fax: 763.847.4010
customerservice@preferredone.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, a Grievance Specialist is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

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Fax: 763.847.4010
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You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

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