MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders**
Policy Number	**2.02.46**
Category	**Technology Assessment**
Original Effective Date	**06/18/15**
Committee Approval Date	**05/25/16, 08/17/17, 05/17/18, 06/20/19, 07/16/20, 11/19/20, 10/28/21, 07/21/22, 09/21/23, 09/19/24**
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Archived Review Date	**N/A**
Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

*****NOTE***This policy does not address the use of whole exome and whole genome sequencing for oncological purposes such as somatic tumor testing and testing for hematologic cancers.*****

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, whole exome sequencing (WES), with trio testing, when possible, may be considered **medically appropriate** for the evaluation of unexplained congenital or neurodevelopmental disorder when **ALL** the following criteria are met:

A. A genetic cause is the most likely explanation for the phenotype despite previous genetic testing (e.g., chromosomal microarray analysis and/or targeted single-gene testing, *(please see Policy Guideline V*) as shown by **TWO** of the following:
1. abnormality affecting at least one organ system;
2. significant developmental or intellectual delay, symptoms of a complex neurodevelopmental disorder, and/or severe neuropsychiatric condition;
3. family history strongly suggesting a genetic etiology;
4. period of unexplained developmental regression;
5. inability to explain symptoms by other causes, such as environmental exposure, injury, or infection; or
6. biochemical findings suggestive of an inborn error of metabolism;

B. **ONE** of the following indications applies:
1. The clinical presentation does not fit a single well-described syndrome, or may describe two or more syndromes making WES more practical than separate single gene tests or panels; or
2. The affected individual is faced with invasive procedures or testing as the next diagnostic step (e.g., muscle biopsy);

C. **ALL** the following indications apply:
1. Medical record documentation reflects that the patient has been evaluated by a clinician with expertise in clinical genetics, and includes at minimum, a family history and phenotype description, and that the patient has been counseled about the potential risks of genetic testing;

2. The diagnosis cannot be established or confirmed by standard clinical work-up; and
3. There is potential for a change in management and clinical outcome for the patient being tested.

II. Based upon our criteria and assessment of the peer-reviewed literature, **ALL** the following genetic tests are considered **investigational** for the diagnosis of genetic disorders:
   A. Whole genome sequencing;
   B. Whole exome sequencing and whole genome sequencing for prenatal diagnosis;
   C. Whole exome sequencing and whole genome sequencing for preimplantation testing of an embryo;
   D. Repeat whole exome sequencing or whole genome sequencing;
   E. Epigenetic assay (e.g., EpiSign [Greenwood Genomic Center, Greenwood SC]).

III. Based upon our criteria and assessment of the peer-reviewed literature, whole mitochondrial genome sequencing, may be considered **medically appropriate** to establish a genetic diagnosis of a mitochondrial disorder when signs and symptoms of a mitochondrial disorder are present and genetic testing may eliminate the need for muscle biopsy.

IV. Based upon our criteria and assessment of the peer-reviewed literature, targeted genetic testing for a known familial variant, may be considered **medically appropriate** to establish a genetic diagnosis of a mitochondrial disorder in at-risk relatives when confirming the diagnosis would alter their medical management/treatment.

POLICY GUIDELINES

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Supporting documentation required:

The following factors will be considered when determining the medical appropriateness of a genetic test:

   A. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.
   B. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.
   C. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).
   D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.
   E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any more extensive/expanded genetic testing such as panel testing. If targeted testing has not been performed, rationale as to why more extensive/expanded genetic testing is medically necessary should be documented.

V. For a request for WES, if no previous genetic testing is completed, we require documentation of a valid justification of why CMA and/or targeted gene testing is not appropriate for the member.

VI. The recommended option for testing when possible is testing of the child and both parents (trio testing). Trio testing

increases the chance of finding a definitive diagnosis and reduces false-positive findings.

VII. The EpiSign assay (Greenwood Genomic Center, Greenwood SC) is a methylation assay designed to readily identify proven and reproducible epigenetic signatures by assessing genome-wide methylation and can detect multiple methylation abnormalities in over 50 genes and disorders.

VIII. The option to receive secondary findings should be offered regardless of the age of the patient. Informed consent should be obtained based on the recommendations of the American College of Medical Genetics and Genomics (ACMG).

Refer to Corporate Medical Policy #2.02.03 Genetic Testing for Inherited Disorders

Refer to Corporate Medical Policy #2.02.42 Chromosomal Microarray (CMA) Analysis for the Prenatal Evaluation and Evaluation of Patients with Developmental Delay/Intellectual Disability or Autism Spectrum Disorder

Refer to Corporate Medical Policy #4.01.03 Prenatal Genetic Testing

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

DESCRIPTION

Individuals may be candidates for whole exome sequencing (WES) when they have features suggestive of an inheritable disease (Mendelian disorder) and diagnostic workup, which may include traditional molecular and conventional diagnostic tests, still yield an inconclusive clinical diagnosis after exhaustive and expensive testing. WES is targeted sequencing of the subset of the human genome that contains functionally important sequences of the protein-coding DNA and comprises approximately 1.5% of the genome and contains approximately 85% of highly penetrant genetic disease DNA variations. To perform whole exome sequence testing, the genomic DNA is hybridized to artificial DNA which is then sequenced with next-generation sequencing (NGS) technology which allows multiple genes to be analyzed at one time and may return a pathogenic variant that is associated with a gene-causing disease. Approximately 85-90% of the exome is covered by whole exome sequencing with less effective coverage in the non-protein-coding portion of the genes. Whole genome sequencing (WGS) processes genomic DNA (both coding and non-coding portions of the gene) followed by a series of computational analyses to determine the sequence of the sample DNA as compared to a reference DNA sequence. WGS is able to evaluate about 90% of the genome and is sequenced similarly to WES by NGS. Whole genome or whole exome sequencing results include three distinct categories: a variant known to cause human diseases, a variant suspected to cause human disease, and a variant of uncertain significance.

Whole exome sequencing has led to the emergence of more than 50 disorders that have been classified as Mendelian disorders, with several of these disorders exhibiting unique genome-wide DNA methylation profiles, known as episignatures. The episignatures are part of a field of study, called epigenetics, which refers to changes in gene expression without altering the primary DNA sequence. Epigenetic modifications include the attachment or removal of a methyl on a cytosine base, or an acetyl group a lysine residue from a histone protein. For the purposes of the type of testing included in this policy, the focus of the epigenetic changes will be on DNA methylation. DNA methylation involves the addition of a methyl group (CH_3), almost exclusively to carbon 5 in a cytosine base, to create 5-methylcytosine. Common sites for DNA methylation are at the promoter or enhancer regions of the affected gene. The addition of the methyl group often prevents transcription or "silences" the gene. DNA hypomethylation involves removing of one or more methyl groups from the cytosine base, which may activate expression of a gene that was previously silenced. Epigenetic changes may be a result of imprinting (specific maternal or paternal gene regulation), from environmental effects on health (e.g., starvation or obesity, stress, smoke, and air pollution), and toxin exposure or ingestion of toxic molecules (e.g., pesticides, plastics, cosmetics). Even though there is a disruption in causative genetic variants in distinct genes, phenotypes in multiple disorders may overlap, making it difficult to make a definitive diagnosis. Common features of the disorders caused by epigenetic changes include intellectual disability, growth defect, and immune dysfunction.

The EpiSign assay (Greenwood Genetic Center, Greenwood, SC), per the Genetic Center website, is an assay designed to readily identify proven and reproducible epigenetic signatures by assessing genome-wide methylation. The assay is a comprehensive analysis of more than 50 genes and disorders and can detect multiple methylation abnormalities associated

with certain imprinting or triplet repeat conditions, as well as identifying disease-specific methylation patterns involving multiple loci across the genome. The assay determines an episignature, a highly sensitive and specific diagnostic biomarker in an increasing number of chromatinopathies, which allows for distinguishing affected from unaffected individuals, disease-causing from non-disease-causing variants. In addition, the assay assesses the functional significance of variations of unknown significance (VUSs), leading to reclassification where applicable. An advantage to the EpiSign assay is that it utilizes a sample from the patient only and the results do not rely on testing of other family members.

Mitochondria are tiny organelles housed in nearly every cell in the body and are responsible for creating cellular energy. Mitochondrial disorders are chronic, genetic conditions that can be inherited and occur when mitochondria fail to produce sufficient energy for the body to function. Mitochondrial diseases can be caused by pathogenic variants in the maternally inherited mitochondrial DNA (mtDNA) or one of many nuclear DNA (nDNA) genes. Nuclear gene variants may be inherited in an autosomal recessive, autosomal dominant, or X-linked manner. Genetic testing for mitochondrial diseases may involve testing for point mutations, deletion, and duplication analysis, and/or whole exome sequencing of nuclear or mtDNA. Primary mitochondrial diseases arise from dysfunction of the mitochondrial respiratory chain which is responsible for aerobic metabolism. This disruption affects a wide variety of physiologic pathways dependent on aerobic metabolism. Most notably, organs with a high-energy requirement, such as the central nervous system, cardiovascular system, and skeletal muscle, are particularly affected by mitochondrial dysfunction.

According to the Mitochondrial Medicine Society consensus statement (Parikh, 2017), the prevalence of these disorders has risen over the last 2 decades as the pathophysiology and clinical manifestations have been better characterized. Mitochondrial diseases are one of the most common inborn errors of metabolism, with a conservative estimated prevalence of approximately 1:5,000. Symptoms can involve one or more organ systems with varying degrees of severity. Each defined mitochondrial disease has a characteristic set of signs or symptoms that may be seen, and mitochondrial disorders can occur at any age. Some specific mitochondrial diseases include Mitochondrial encephalopathy with lactic acidosis and stroke-like symptoms (MELAS) syndrome, Myoclonic epilepsy with ragged-red fibers syndrome (MERFF), Kearns-Sayre syndrome, Leigh syndrome, Chronic progressive external ophthalmoplegia (CPEO), Leber hereditary optic neuropathy (LHON), and Neuropathy, ataxia, and retinitis pigmentosa (NARP). Individuals may not fit into a specific category of symptoms and may exhibit common symptoms such as ataxia, cardiomyopathy, diabetes mellitus, exercise intolerance, external ophthalmoplegia, fluctuating encephalopathy, myopathy, optic atrophy, pigmentary retinopathy, ptosis, seizures, sensorineural deafness, and spasticity.

RATIONALE

Published exome sequencing studies show that the technology can be used to detect previously cataloged pathogenic mutations and reveal new likely pathogenic mutations in known and unknown genes. In addition, WES appears to have a higher diagnostic yield, to have quicker return of results, and to be more efficient compared to traditional Sanger sequencing.

The American College of Medical Genetics (ACMG) has stated that diagnostic testing with WES (and WGS) should be considered in the clinical diagnostic assessment of a phenotypically affected individual when:

I. 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.
II. 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.
III. A patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to arrive at a diagnosis.
IV. A fetus has a likely genetic disorder, but specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis.

The ACMG recommends that WGS/WES may be considered in preconception carrier screening, using a strategy to focus on genetic variants known to be associated with significant phenotypes in homozygous or hemizygous progeny.

The ACMG also recommends that WGS/WES should not be used at this time as an approach to prenatal screening, or as a

first-tier approach for newborn screening.

In March 2013, an ACMG board finalized approval of its recommendations for reporting incidental findings in WGS and WES. A working group determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing. The group recommended that, when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes, and variants be routinely evaluated and reported to the ordering clinician.

In 2021, Miller et al. published the ACMG's updated recommendations for reporting of secondary finding in clinical exome and genome sequencing. In addition to policy updates and recommendations by the ACMG's Secondary Finding Maintenance Working Group (SFWG), they announced plans to update the list of actionable secondary findings annually. According to the statement, "the option to receive secondary findings should be offered regardless of the age of the patient. The best interest of the child should still be prioritized when disclosing risk for adult-onset conditions in minors."

Literature for re-analysis of WES is limited and no randomized controlled trials were identified. One systematic review and meta-analysis (Dai et al., 2022) aimed to determine the diagnostic yield, optimal timing, and methodology of next generation sequencing data reanalysis in suspected Mendelian disorders. They included 29 studies in their analysis of patients whose initial WES or WGS produced a negative result with no diagnosis. Significant heterogeneity was noted between studies. Reanalysis had an overall diagnostic yield of 0.10 (95% CI = 0.06-0.13). Literature updates accounted for most new diagnoses. Diagnostic yield was higher after 24 months, although this was not statistically significant. Increased diagnoses were obtained with research validation and data sharing. AI-based tools did not adversely affect reanalysis diagnostic rate. Due to the heterogeneity of the studies, the optimal time to reanalysis and the impact of AI-based tools could not be determined with confidence. The available literature does not report a change in medical management of the patient or demonstrate improved patient outcomes. The optimal timing of re-analysis has not been established, and there are no clear guidelines on what factors should prompt the decision to repeat testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Laboratories may offer re-analysis of WES or WGS data within a few years of original testing for previous patients.

ACMG published a series of points to consider regarding the reevaluation and reanalysis of genomic test results at various levels (Deignan, 2019). It recommends a periodic variant-level reevaluation and case-level reanalysis. In addition, for cases remaining unsolved, it is useful to keep updated phenotypic descriptions to improve the specificity of the phenotype, because this can help to increase the diagnostic yield as well. Clinical laboratories should make concerted efforts to prioritize the reporting and communication of any reclassifications that may affect clinical management. For example, a variant of uncertain clinical significance that is reclassified as a likely pathogenic variant should be prioritized as compared to a likely pathogenic variant that is reclassified as a pathogenic variant. Clinical laboratories should also consider the reporting and communication of any variants of uncertain clinical significance that are reclassified to likely benign or benign, as these reclassifications may also have an impact on clinical management.

Many summary articles and reviews have been published regarding the use of epigenetics in describing and diagnosing neurodevelopmental and certain Mendelian disorders. However, the mechanistic understanding of multigenerational phenotypes and DNA methylation are still not clearly defined. Further studies and improved methods are needed to explain mechanisms of action of environmental factors, gene-environment interactions, and multigenerational effects. The results of these studies may expand our knowledge and help to identify biomarkers and risk factors for disease and improve diagnostic and treatment practices. Currently there are no Medical Society Guidelines recommending testing for episignatures in these disorders.

For individuals with signs and/or symptoms of a mitochondrial disease who receive genetic testing, the evidence includes case series and cohort studies. There is some evidence on clinical validity that varies by the patient population and testing strategy. Studies reporting diagnostic yield for known pathogenic variants using NGS panels tend to report rates ranging from 15% to 25%. Clinical utility is relatively high for confirming the diagnosis of mitochondrial diseases in people who have signs and symptoms of the disease. In these patients, a positive result in genetic testing can avoid a muscle biopsy and eliminate the need for further clinical workup. A prospective cohort study by Riley et al. (2020) performing mitochondrial testing for 40 children with suspected mitochondrial disease. A likely molecular diagnosis was identified in

67% of cases and a definitive molecular diagnosis achieved in 55% of cases. Diagnosis reportedly to lead to improved patient outcomes and medical management of the participants and their families. For individuals who are asymptomatic with a close relative with a mitochondrial disease and a known pathogenic variant and who receive targeted familial variant testing, genetic testing may impact reproductive decision-making.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
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); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)

Code	Description
81425 (E/I)	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426 (E/I)	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
81427 (E/I)	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
81440	Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
81460	Whole mitochondrial genome (e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
81465	Whole mitochondrial genome large deletion analysis panel (e.g., Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
0094U (E/I)	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis (RCIGM Rapid Whole Genome Sequencing, Rady Children's Institute for Genomic Medicine (RCIGM))
0209U (E/I)	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes, and areas of homozygosity for chromosomal abnormalities (CNGnome, PerkinElmer Genomics)
0212U (E/I)	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 (Genomic Unity® Whole Genome Analysis – Proband, Variantyx Inc, Variantyx Inc)
0213U (E/I)	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 (e.g., parent, sibling) (Genomic Unity® Whole Genome Analysis – Comparator, Variantyx Inc)

Code	Description
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 (Genomic Unity Exome Plus Analysis – Proband, Variantyx Inc)
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 (e.g., parent, sibling) (Genomic Unity® Exome Plus Analysis – Comparator, Variantyx Inc.)
0265U (E/I)	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 (Praxis Whole Genome Sequencing, Praxis Genomics LLC)
0318U (E/I)	Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood (EpiSign Complete, Greenwood Genetic Center)
0335U (E/I)	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 (IriSight™ Prenatal Analysis – Proband, Variantyx, Inc)
0336U (E/I)	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 (e.g., parent) (IriSight™ Prenatal Analysis – Comparator, Variantyx, Inc)
0417U	Rare diseases (constitutional/heritable disorders), whole mitochondrial genome sequence with heteroplasmy detection and deletion analysis, nuclear-encoded mitochondrial gene analysis of 335 nuclear genes, including sequence changes, deletions, insertions, and copy number variants analysis, blood or saliva, identification, and categorization of mitochondrial disorder-associated genetic variants (Genomic Unity® Comprehensive Mitochondrial Disorders Analysis, Variantyx Inc)
0425U (E/I)	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (e.g., parents, siblings) (RCIGM Rapid Whole Genome Sequencing, Comparator Genome, Rady Children's Institute for Genomic Medicine) (effective 01/01/24)
0426U (E/I)	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis (RCIGM Ultra-Rapid Whole Genome Sequencing, Rady Children's Institute for Genomic Medicine) (effective 01/01/24)

Code	Description
0469U (E/I)	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 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 (IriSight™ CNV Analysis, Variantyx Inc) (effective 07/01/24)
0532U (E/I)	Rare diseases (constitutional disease/hereditary disorders), rapid whole genome and mitochondrial DNA sequencing for single-nucleotide variants, insertions/deletions, copy number variations, peripheral blood, buffy coat, saliva, buccal or tissue sample, results reported as positive or negative (effective 04/01/25)
0567U (E/I)	Rare diseases (constitutional/heritable disorders), whole-genome sequence analysis combination of short and long reads, for single-nucleotide variants, insertions/deletions and characterized intronic variants, copy-number variants, duplications/deletions, mobile element insertions, runs of homozygosity, aneuploidy, and inversions, mitochondrial DNA sequence and deletions, short tandem repeat genes, methylation status of selected regions, blood, saliva, amniocentesis, chorionic villus sample or tissue, identification and categorization of genetic variants (effective 07/01/25)

HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
Numerous Diagnoses	

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*Key Article

KEY WORDS

Exome, genome, WES, WGS

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures (L35000). Please refer to the following LCD website for Medicare members:

[https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=144&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AggAAAQAgAAA&=] accessed 08/08/24.

There is currently a Local Coverage Article (LCA) for Billing and Coding: Molecular Pathology Procedures (A56199). Please refer to the following LCA website for Medicare members:

[https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199&ver=102&keyword=81415&keywordType=starts&areaId=s41&docType=NCA%2CCAL%2CNCD%2CMEDCAC%2CTA%2CMCD%2C6%2C3%2C5%2C1%2CF%2CP&contractOption=all&sortBy=relevance&bc=1] accessed 08/08/24.