MEDICAL POLICY

Medical Policy Title	**Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders**
Policy Number	**2.02.46**
Current Effective Date	**September 18, 2025**
Next Review Date	**September 2026**

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

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.

I. Whole exome sequencing (WES), with trio testing, when possible, may be considered **medically appropriate** for the evaluation of an 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** (2) of the following:

1. Abnormality affecting at least one (1) 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. **EITHER** of the following indications applies:

1. The clinical presentation does not fit a single well-described syndrome, or may describe two (2) 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. 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.

III. 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.

IV. **ALL** of 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]).

RELATED POLICIES

Corporate Medical Policy

2.02.03 Genetic Testing for Inherited Disorders

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

4.01.03 Prenatal Genetic Testing

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

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 90 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).

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.

SUPPORTIVE LITERATURE

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.

Sánchez Suárez et al (2024) conducted an observational, prospective study to determine the diagnostic yield of WES with targeted gene panels in children with neurodevelopmental disorders (NDDs). The study included a total of 176 Spanish-speaking pediatric patients with neurodevelopmental disorders (NDDs), encompassing intellectual disability (ID) (n=67 [38.1%]), global developmental delay (GDD), and/or autism spectrum disorder (ASD) (n=62 [35.2%]) and ASD + ID (n=47 [26.7%]). Participants were recruited from January 2019 to January 2023 at a University Hospital in Madrid, Spain. Clinical and sociodemographic variables were recorded, along with genetic study results. The age range of the subjects was 9 months to 16 years, and the percentage of males was 72.1%. The diagnostic yield of WES was calculated both before and after parental testing via Sanger DNA sequencing. The diagnostic yield of proband-only exome sequencing was 12.5% (22/176). By group, the diagnostic yield of proband-only exome sequencing was 3.2% in the ASD, 12.7% in the ASD + ID, and 20.8% in the ID group. Variants of uncertain significance (VUS) were found in 39.8% (70/176). After parental testing, some variants were reclassified as "likely pathogenic", increasing the diagnostic yield by 4.6%, with an overall diagnostic yield of 17.1%. Diagnostic yield was higher in patients with syndromic ID (70.6%% versus 29.4%; p = 0.036). The authors concluded this study shows a sequential approach utilizing WES followed by panel-based analysis, starting with the index case and, when appropriate, including the parents, proves to be a cost-effective strategy. WES is particularly suitable for complex conditions, as it allows for the identification of potentially causative genes beyond those covered by targeted panels, providing a more comprehensive analysis. Including parental testing enhances the diagnostic yield and improves accuracy, especially in cases with variants of uncertain significance (VUS), thereby advancing our understanding of NDDs.

A randomized controlled trial was conducted with the aim of determining the effect of WGS on clinical management in a racially and ethnically diverse and geographically distributed population of acutely ill infants in the United States (NICUSeq 2021). This time-delayed clinical trial enrolled participants from September 11, 2017, to April 30, 2019, with an observation period extending to July 2, 2019. The study was conducted at five (5) US academic medical centers and affiliated children's hospitals. Participants included infants aged between 0 and 120 days who were admitted to an intensive care unit with a suspected genetic disease. Data were analyzed from January 14 to August 20, 2020. Patients were randomized to receive clinical WGS results 15 days (early) or 60 days (delayed) after enrollment, with the observation period extending to 90 days. Usual care was continued throughout the study. The main outcome was the difference in the proportion of infants in the early and delayed groups who received a change of management (COM) 60 days after enrollment. Additional outcome measures included WGS diagnostic efficacy, within-group COM at 90 days, length of hospital stay, and mortality. A total of 354 infants were randomized to the early (n=176) or delayed (n=178) arms. The mean participant age was 15 days (IQR, 7-32 days); 201 participants (56.8%) were boys; 19 (5.4%) were Asian; 47 (13.3%) were Black; 250 (70.6%) were White; and 38 (10.7%) were of another race. At 60 days, twice as many infants in the early group vs the delayed group received a COM (34 of 161 [21.1%; 95% CI, 15.1%-28.2%] versus 17 of 165 [10.3%; 95% CI, 6.1%-16.0%]; P=.009; odds ratio, 2.3; 95% CI, 1.22-4.32) and a molecular diagnosis (55 of 176 [31.0%; 95% CI, 24.5%-38.7%] vs 27 of 178 [15.0%; 95% CI, 10.2%-21.3%]; P<.001). At 90 days, the delayed

group showed a doubling of COM (to 45 of 161 [28.0%; 95% CI, 21.2%-35.6%]) and diagnostic efficacy (to 56 of 178 [31.0%; 95% CI, 24.7%-38.8%]). The most frequent COMs across the observation window were subspecialty referrals (39 of 354; 11%), surgery or other invasive procedures (17 of 354; 4%), condition-specific medications (9 of 354; 2%), or other supportive alterations in medication (12 of 354; 3%). No differences in length of stay or survival were observed. The authors concluded the RCT showed that the introduction of WGS was associated with a significant increase in focused clinical management compared with usual care for acutely ill infants in an intensive care unit. Access to first-line WGS may reduce health care disparities by enabling diagnostic equity. These data support WGS adoption and implementation in this population.

A meta-analysis was conducted to assess whether WGS, for the pediatric population with suspected genetic disorders, is cost-effective with respect to WES and chromosomal microarray (CMA) by pooling incremental net benefits (Nurchis 2022). Articles from 2015 to 2021 were analyzed with four (4) meeting inclusion criteria. The dominance ranking matrix (DRM) tool was adopted to provide a qualitative synthesis of all the included studies. Incremental net benefits (INBs) were estimated, and meta-analysis was implemented to pool INBs across studies. The pooled INB of WGS over WES was estimated at I$4073 (95% CI I$2426 - I$5720). The pooled INB of WGS over CMA amounted to I$6003 (95% CI I$2863 - I$9143). Limitations of the meta-analysis include the small number of studies included and the high heterogeneity detected (I^2= 92.8% for WGS versus WES and I^2=98.49% for WGS versus CMA) across the pooled INBs. The authors concluded that this meta-analysis showed WGS could be cost-effective in the diagnostic workup of affected infants and children. Further economic evaluations however are needed for comparing WGS versus WES and confirm the present conclusions.

Shreeve et al (2024) conducted a meta-analysis to determine the incremental yield of WGS over quantitative fluorescence polymerase chain reaction (QF-PCR)/chromosomal microarray analysis (CMA) with and without exome sequencing (ES) in fetuses, neonates and infants with a congenital anomaly that was or could have been detected on prenatal ultrasound. Secondly, they aimed to evaluate the turnaround time (TAT), and quantity of DNA required for testing using these pathways. Articles from January 2010 to December 2022 were assessed for inclusion criteria which included cohort studies with three (3) or more fetuses, neonates or infants with (i) one (1) or more congenital anomalies; (ii) an anomaly which was or would have been detectable on prenatal ultrasound; and (iii) negative QF-PCR and CMA. Pooled incremental yield was determined using a random-effects model and heterogeneity was assessed using Higgins' I^2 test. Sub analyses were performed based on pre- or postnatal cohorts, cases with multisystem anomalies and those meeting the NHS England prenatal ES inclusion criteria. A total of 18 studies incorporating 902 eligible cases were included, of which eight (44.4%) studies focused on prenatal cohorts, incorporating 755 cases, and the remaining studies focused on fetuses undergoing postmortem testing or neonates/infants with congenital structural anomalies, constituting the postnatal cohort. The incremental yield of WGS over QF-PCR/CMA was 26% (95% CI, 18-36%) (I^2=86%), 16% (95% CI, 9-24%) (I^2=85%) and 39% (95% CI, 27-51%) (I^2=53%) for all, prenatal and postnatal cases, respectively. The incremental yield increased in cases in which sequencing was performed in line with the NHS England prenatal ES criteria (32% (95% CI, 22-42%); I^2=70%) and in those with multisystem anomalies (30% (95% CI,

19-43%); I^2=65%). The incremental yield of WGS for variants of uncertain significance (VUS) was 18% (95% CI, 7-33%) (I^2=74%). The incremental yield of WGS over QF-PCR/CMA and ES was 1% (95% CI, 0-4%) (I^2=47%). The pooled median TAT of WGS was 18 (range, 1-912) days, and the quantity of DNA required was 100 ± 0 ng for WGS and 350 ± 50 ng for QF-PCR/CMA and ES (P=0.03). The authors concluded this meta-analysis showed WGS in cases with congenital anomaly holds great promise, though incremental yield over ES is yet to be demonstrated. However, the laboratory pathway for WGS required less DNA with a potentially faster TAT compared with sequential QF-PCR/CMA and ES. There was a high rate of VUS using WGS.

Literature for re-analysis of WES is limited, and no randomized controlled trials were identified. One systematic review and meta-analysis (Dai 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.

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.

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.

PROFESSIONAL GUIDELINE(S)

The American College of Medical Genetics (ACMG) policy statement (2012) of points to consider in the clinical application of genomic sequencing states 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.

ACMG published evidenced-based clinical guidelines for exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability (2021) states the following:

- "We strongly recommend ES and GS as a first-tier or second-tier test (guided by clinical judgment and often clinician–patient/ family shared decision making after CMA or focused testing) for patients with one or more [congenital anomalies] CAs prior to one year of age or for patients with[developmental delay/intellectual delay] DD/ID with onset prior to 18 years of age."
- "ES/GS demonstrates clinical utility for the patients and their families with limited evidence for negative outcomes and the ever increasing emerging evidence of therapeutic benefit."

The American Academy of Pediatrics (AAP) published their clinical report for the genetic evaluation of the child with ID or global developmental delay (GDD) and recommend the following (Rodan 2025):

- recommends exome/genome sequencing as a first-tier test for GDD/ID in most circumstances because of superior diagnostic yield and higher cost-effectiveness if pursued earlier in the diagnostic process.
- Genome sequencing has been demonstrated to provide an approximately 10% to 20% higher diagnostic yield than exome sequencing, so it is preferable but currently may be less accessible to providers to order than exome sequencing.
- The diagnostic yield of exome/ genome sequencing is improved if a trio sample is sent (proband and both parents), because this can determine de novo variants and can establish the phase of biallelic variants.
- Limitations of exome/genome sequencing include inability to diagnose repeat disorders and

methylation abnormalities.

- If a more targeted GDD/ID panel is nondiagnostic, then exome/genome sequencing may be considered next.
- The third tier includes consideration of genome sequencing if exome sequencing was previously performed and mitochondrial DNA (mtDNA) testing if not included with prior testing.
- If negative, exome/genome sequencing may be clinically reanalyzed every 1 to 2 years following the initial test.

In March 2013, an ACMG board finalized approval of its recommendations for reporting incidental findings in WGS and WES (Green 2013). 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.

ACMG updated recommendations for reporting of secondary finding in clinical exome and genome sequencing (Miller 2023). 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.

ACMG published a series of points to consider regarding the reevaluation and reanalysis of genomic test results at various levels (Deignan 2019). They recommend 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.

Currently there are no Medical Society Guidelines recommending testing for episignatures in these disorders.

The Mitochondrial Medicine Society (Parikh 2015) published a consensus statement on the diagnosis and management of mitochondrial disease. Most evidence was grade III or less (case-control, low-quality cohort studies, or expert opinion without an explicit critical appraisal). A subset of the consensus recommendations for DNA testing are as follows:

- Massively parallel sequencing/NGS [next-generation sequencing] of the mtDNA [mitochondrial DNA]genome is the preferred methodology when testing mtDNA and should be performed in cases of suspected mitochondrial disease instead of testing for a limited number of pathogenic

point mutations.

- mtDNA deletion and duplication testing should be performed in cases of suspected mitochondrial disease via NGS of the mtDNA genome, especially in all patients undergoing a diagnostic tissue biopsy.
    - If a single small deletion is identified using polymerase chain reaction-based analysis, then one should be cautious in associating these findings with a primary mitochondrial disorder.
    - When multiple mtDNA deletions are noted, sequencing of nuclear genes involved in mtDNA biosynthesis is recommended.
- When considering nuclear gene testing in patients with likely primary mitochondrial disease, NGS methodologies providing complete coverage of known mitochondrial disease genes is preferred. Single-gene testing should usually be avoided because mutations in different genes can produce the same phenotype. If no known mutation is identified via known NGS gene panels, then whole exome sequencing should be considered.

A 2020 Health Technology Assessment conducted by Ontario Health, included a comparative review of the diagnostic yield of WES and WGS in children with unexplained developmental disabilities or multiple congenital anomalies (Ontario Health 2020). The diagnostic yield across all studies was 37% (95% CI, 34% to 40%). More studies, with an overall larger sample size, were included in the examination on WES (34 studies, n=9142) than on WGS (9 studies, n=648). Confidence intervals for studies using WES versus WGS overlapped (37%; 95% CI, 34% to 40%, versus 40%; 95% CI, 32% to 49%). Diagnostic yield ranged between 16% and 73%, with variation attributed largely to technology used and participant selection. The overall quality of the evidence was rated as very low, downgraded for risk of bias, inconsistency, indirectness, and imprecision.

The American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine published a joint committee opinion (Committee on Genetics 2016; reaffirmed 2025) regarding the use of advanced genetic diagnostic tools in obstetrics and gynecology. They stated the following regarding prenatal WES and WGS:

- "The routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Whole exome sequencing or WGS tests as a clinical service are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

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)

Code	Description
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)
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)

Code	Description
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)
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)

Code	Description
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)
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)
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)
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 (Rapid Genome Sequencing Test, University of California San Francisco Genomic Medicine Laboratory) (effective 04/01/25)

Code	Description
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 (Genomic Unity 2.0, Variantyx Inc, Variantyx Inc) (effective 07/01/25)
0582U (E/I)	Rare diseases (constitutional disease/hereditary disorders), rapid whole genome DNA sequencing for single-nucleotide variants, insertions/deletions, copy number variations, blood, saliva, tissue sample, variants reported (Rapid Whole Genome Sequencing, Mayo Clinic, Mayo Clinic) (effective 10/1/25)
0583U (E/I)	Rare diseases (constitutional disease/hereditary disorders), rapid whole genome comparator DNA sequencing for single-nucleotide variants, insertions/deletions, copy number variations, blood, saliva, tissue sample, variants reported with proband results (List separately in addition to code for primary procedure) (Rapid Genome Sequencing Family Member Comparator, Mayo Clinic, Mayo Clinic) (effective 10/1/25)

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
Multiple Codes	

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SEARCH TERMS

Exome, genome, WES, WGS

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Molecular Pathology Procedures (LCD L35000) [accessed 2025 Aug 7]

Billing and Coding: Molecular Pathology Procedures (Article A56199) [accessed 2025 Aug 7]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, 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.

POLICY HISTORY/REVISION

Committee Approval Dates

06/18/15, 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, 09/18/25

Date	Summary of Changes
09/30/25	• Off-cycle policy review, code edit, added CPT codes 0582U and 0583U. Policy intent unchanged.

09/18/25	• Annual review, policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
06/18/15	• Original effective date