Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions) (for New Mexico Only)

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➲ Instructions for Use

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Related Policies

- Chromosome Microarray Testing (Non-Oncology Conditions) (for New Mexico Only)
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- Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions (for New Mexico Only)
- Preimplantation Genetic Testing and Related Services (for New Mexico Only)

Application

This Medical Policy only applies to the state of New Mexico.

Coverage Rationale

Genetic counseling is strongly recommended prior to Whole Exome Sequencing or Whole Genome Sequencing in order to inform persons being tested about the advantages and limitations of the test as applied to their unique situation.

Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS), with or without concurrent Comparator Analysis, is proven and medically necessary when all of the following criteria are met:

- The affected individual displays signs or symptoms of an undiagnosed or unexplained disorder with a suspected genetic cause
- Test results are intended to directly impact the individual's medical management
- The clinical presentation does not fit a Well-Delineated Genetic Syndrome or disorder for which a specific test or a Targeted Panel test is available (if a specific genetic syndrome is suspected, a single gene or Targeted Panel should be performed prior to determining if WES or WGS is necessary)
- The test is ordered by a medical geneticist, neonatologist, neurologist, immunologist, or developmental pediatrician
- The clinical presentation includes:
  - **One** or more of the following:
    - Multiple Congenital Anomalies affecting at least two different organ systems
    - Intellectual Disability characterized as moderate, severe, or profound, diagnosed by 18 years of age
    - Global Developmental Delay
    - Epileptic Encephalopathy with onset before three years of age

    or
  - **Two** or more of the following:
    - Congenital Anomaly
    - Significant hearing or visual impairment diagnosed by 18 years of age

- Laboratory abnormalities suggestive of an inborn error of metabolism
- Autism Spectrum Disorder
- Neuropsychiatric condition (e.g., bipolar disorder, schizophrenia, obsessive-compulsive disorder)
- Hypotonia or hypertonia in infancy
- Dystonia, ataxia, hemiplegia, neuromuscular disorder, movement disorder, or other serious neurologic abnormality
- Unexplained developmental regression unrelated to Autism Spectrum Disorder or epilepsy
- Growth abnormality (e.g., failure to thrive, short stature, microcephaly, macrocephaly, or overgrowth)
- Persistent and severe immunologic or hematologic disorder
- Dysmorphic features
- Consanguinity
- Other first- or second-degree family member(s) with similar clinical diagnosis

Non-concurrent Comparator Analysis for WES or WGS is proven and medically necessary when both of the following criteria are met:
- The affected individual meets the above criteria for WES or WGS
- WES or WGS has been previously performed on the affected individual

Reanalysis of WES or WGS data is proven and medically necessary when all of the following criteria are met:
- At least 18 months have passed since the initial WES or WGS was performed
- The affected individual meets the above criteria for WES or WGS
- Either of the following occurs:
  - The affected individual experiences additional symptoms after initial WES or WGS that cannot be explained by the results of the initial testing
  - New data or new family history emerges which suggests a link between the individual's symptoms and specific genes

Prenatal WES is proven and medically necessary for diagnosing or evaluating a genetic disorder when all of the following criteria are met:
- Chromosome microarray analysis (CMA) and/or karyotyping has been performed but was uninformative
- WES is ordered by or in consultation with a medical geneticist or maternal-fetal medicine specialist (perinatologist)
- The specimen is obtained from amniotic fluid and/or chorionic villi, or DNA is extracted from fetal blood or tissue
- The fetus has one or more of the following:
  - Multiple Congenital Anomalies affecting at least two different organ systems
  - Fetal hydrops of unknown etiology
  - A Congenital Anomaly affecting a single organ system and family history that suggests a genetic etiology

Due to insufficient evidence of efficacy, WES is unproven and not medically necessary for all other indications including but not limited to the following:
- Evaluation of fetal demise
- Prenatal testing via cell-free fetal DNA
- Preimplantation Genetic Testing (PGT) in embryos
- Screening and evaluating disorders in individuals when the above criteria are not met

Due to insufficient evidence of efficacy, WGS is unproven and not medically necessary for all other indications including but not limited to the following:
- Evaluation of fetal demise
- Preimplantation Genetic Testing (PGT) in embryos
- Prenatal genetic diagnosis or screening
- Screening and evaluating disorders in individuals when the above criteria are not met

The use of rapid Whole Exome Sequencing (rWES), rapid Whole Genome Sequencing (rWGS), or ultra-rapid Whole Genome Sequencing (urWGS) is unproven and not medically necessary for use in outpatient settings.

Whole transcriptome sequencing, epigenetic signature analysis, and optical genome mapping (OGM) are considered unproven and not medically necessary for any indication due to insufficient evidence of efficacy.

Note: The evaluation of cancer is addressed in the Medical Policies titled Molecular Oncology Testing for Solid Tumor Cancer Diagnosis, Prognosis, and Treatment Decisions (for New Mexico Only), Molecular Oncology Testing for

Hematologic Cancer Diagnosis, Prognosis, and Treatment Decisions (for New Mexico Only), and FDA Cleared or Approved Companion Diagnostic Testing (for New Mexico Only).

Additionally, this policy for *Whole Exome and Whole Genome Sequencing (Non-Oncology Conditions)* is applicable only to testing in an outpatient setting or upon discharge from an inpatient setting.

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the federal, state, or contractual requirements, and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the services requested.

The patient's medical record must contain documentation that fully supports the medical necessity for the requested services. This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available upon request.

Definitions

Refer to the federal, state, or contractual definitions that supersede the definitions below.

Autism Spectrum Disorder: A condition marked by enduring problems communicating and interacting with others, along with restricted and repetitive behavior, interests, or activities and as listed in the current edition of the International Classification of Diseases section on Mental and Behavioral Disorders or the Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association (UnitedHealthcare Insurance Company Generic Certificate of Coverage, 2025).

Comparator Analysis: Genetic evaluation of an individual's close relative(s) to aid in the interpretation of the individual's test results. Typically, this involves a child and their biological parents and is also known as trio testing (Deignan et al., 2020).

Congenital Anomaly: A physical developmental defect that is present at the time of birth and that is identified within the first twelve months of birth (UnitedHealthcare Insurance Company Generic Certificate of Coverage, 2025).

Consanguinity: Procreation with second-cousins or closer (Bennett et al., 2021).

Epileptic Encephalopathy: Epileptic seizures in the setting of frequent epileptiform activity on electroencephalography (EEG) that result in developmental slowing or regression (Scheffer et al., 2025).

Global Developmental Delay: The failure to meet expected developmental milestones in several areas of intellectual functioning in an individual younger than 5 years of age (American Psychiatric Association, 2013).

Intellectual Disability: A neurodevelopmental disorder that begins in childhood, characterized by intellectual difficulties as well as difficulties in conceptual, social, and practical areas of living (American Psychiatric Association, 2013).

Preimplantation Genetic Testing (PGT): A test performed to analyze the DNA from oocytes or embryos for human leukocyte antigen (HLA)-typing or for determining genetic abnormalities (UnitedHealthcare Insurance Company Generic Certificate of Coverage, 2025).

Targeted Panel: A curated assay that simultaneously tests more than one gene associated with a condition. A Targeted Panel may consist of multiple genes that are associated with one specific genetic condition or multiple genes that are associated with a symptom or non-specific clinical presentation (Rehder et al., 2021).

Well-Delineated Genetic Syndrome: A syndrome is a collection of recognizable traits or abnormalities that tend to occur together and are associated with a specific disease. Distinguishing characteristics, such as specific facial features or other physical traits, lab tests, or family history can be used to identify a genetic syndrome (Talking Glossary of Genomic and Genetic Terms, 2025).

Whole Exome Sequencing (WES): About 1% of a person's DNA makes protein. These protein making sections are called exons. All the exons together are called the exome. WES is a DNA analysis technique that looks at all of the exons in a person at one time, rather than gene by gene (MedlinePlus, 2020).

Whole Genome Sequencing (WGS): WGS determines the sequence of all of the DNA in a person, which includes the protein making (coding) as well as non-coding DNA elements (MedlinePlus, 2020).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0094U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., 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 categorization of genetic 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 categorization of genetic variants, each comparator exome (e.g., parent, sibling)
0260U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
0264U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
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
0266U	Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression change
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
0318U	Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood
0335U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants

CPT Code	Description
0336U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., parent)
0425U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (e.g., parents, siblings)
0426U	Genome (e.g., unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis
0454U	Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping
0469U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of 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
0528U	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
0532U	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
0538U	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)
0567U	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
81354	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of structural and copy number variants, optical genome mapping (OGM)
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)
81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	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	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)

Description of Services

Whole Exome Sequencing (WES) refers to the sequence determination of the exome. The exome is the portion of an individual's genome that encodes protein (also known as exons). Exons make up approximately 1-2% of the genome

(Chung, 2023). Most known disease-causing variants are found in the exons, and by sequencing them all simultaneously, a more efficient analysis can be completed than by sequencing each individual gene alone (Bertier et al., 2016). WES results in long lists of genetic variants. The success of this technology is dependent on how consistently and accurately labs can identify disease causing mutations (Richards et al., 2015).

Whole Genome Sequencing (WGS) determines the order of all the nucleotides in an individual's DNA and can determine variations in any part of the genome (MedlinePlus, 2020). This provides the potential to detect disease-causing copy number variants (CNVs) and structural variants (SVs), repeat expansions, and nonexonic regulatory and splicing variations (Chung, 2023). As with WES, WGS results in long lists of unknown variants. The methodology and databases available to interpret WGS are the same as WES and focus primarily on the exons (Richards et al., 2015; Landrum et al., 2016).

Whole transcriptome sequencing, identifies and characterizes both coding and noncoding ribonucleic acid (RNA). To carry out the instructions housed in the base pairs of chemicals making up an individual's genes, DNA must be transcribed into RNA. These "readouts" of genes are called transcripts. A transcriptome is the collective of all the gene readouts in a cell (National Human Genome Research Institute, 2020). Whole transcriptome sequencing analyzes all of the sequences of RNA present in a tissue and has the ability to provide additional and/or different information than can be obtained from DNA-based sequencing. Use of this technology has been proposed for multiple clinical purposes, including rare genetic diseases and oncology indications.

Optical genome mapping (OGM) uses technology such as high-resolution microscopy, automated image analysis, and microfluidics to image very long, linear single DNA molecules in which labels have been placed at specific sites to construct a genome "map" of the sample under study along with a reference sample. This can be used to identify SVs in the genome, including insertions, deletions, duplications, inversions, and translocations, even when these variations are very small. The current paradigm for detection of SVs is standard cytogenetics which have lower resolution and are not able to detect balanced SVs or genomic location and orientation of insertions or duplications (Mantere et al., 2021). OGM is currently being studied for potential application in human genetic diagnostics.

Epigenetic signature analysis evaluates the interaction of DNA letters and the proteins that interact with them to cause chemical modifications. These modifications result in genes that are turned on or off and may impact an individual's health (Talking Glossary of Genomic and Genetic Terms, 2025). Epigenetic signature analysis is currently being studied for potential clinical applications.

Clinical Evidence

Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS)

A systematic review and meta-analysis by Albuquerque et al. (2025) evaluated the diagnostic yield of genome sequencing (GS) compared to exome sequencing (ES) and ES reanalysis in children with rare phenotypes. The authors searched PubMed, Embase, and Cochrane databases through December 11, 2024 and included 12 nonrandomized studies, 110of which were included in the meta-analysis, encompassing 1684 children who underwent GS after negative ES. The pooled GS-specific diagnostic yield (defined as diagnoses that could only be made by GS) was 7.0% (95% CI: 5.1%–9.5%; $p < 0.0001$). In a subset of 1610 individuals, ES reanalysis yielded a diagnostic rate of 14.2% (95% CI: 8.9%–21.8%; $p < 0.0001$), while the total GS diagnostic yield in the same cohort was 24.1% (95% CI: 17.6%–31.9%; $p = 0.0239$). Subgroup analysis of 1145 individuals with neurodevelopmental phenotypes showed a GS-specific diagnostic yield of 5.3% (95% CI: 3.1%–9.6%). The authors concluded that GS can identify additional diagnoses in 7.0% of children after negative ES, but ES reanalysis and GS showed statistically similar diagnostic yields, highlighting the value of periodic ES reanalysis in clinical workflows. The study's limitations include inconsistent reporting of clinical utility outcomes by each study, lack of subgroup analysis by sequencing strategy (singleton, duo, trio), and limited representation of long-read GS technologies. The heterogeneity among studies limits the generalizability and practical application of the findings. Publications by AlAbdi et al. (2023), Alfares et al. (2018), Guo et al. (2024), Sun et al. (2022), and Wojcik et al. (2024), previously discussed in this policy, were included in the Albuquerque systematic review.

A systematic literature review and meta-analysis by Pandey et al. (2025) evaluated the diagnostic yield and clinical utility of GS and ES in children with rare and undiagnosed genetic diseases. The study included 108 studies (106 unique) published between 2011 and 2023, comprising 24,631 probands under 18 years of age. Comparative analyses focused on within-cohort studies using random-effects models. The pooled diagnostic yield was 34.2% for GS or ES, versus 18.1% for non-GWS [i.e., single or panel gene sequencing or chromosomal microarray (CMA)], with 2.4-times higher odds of diagnosis (95% CI: 1.40–4.04; $p < .05$). In three within-cohort studies comparing GS and ES, the trend was toward higher diagnostic yield for GS than ES (30.6% vs. 23.2%), with 1.7-times higher odds of diagnosis for GS (95% CI: 0.94–

2.92; p = .13), which was not statistically significant. The pooled clinical utility among individuals with a positive diagnosis was 58.7% for GS and 54.5% for ES. The proportion of individuals with variants of uncertain significance (VUSs) was 9.8% for GS and 8.0% for ES. The authors concluded that GS appears to have a higher diagnostic yield than ES, with similar clinical utility per positive diagnosis. However, substantial heterogeneity across studies, particularly in single-arm analyses, and variability in clinical utility definitions pose threats to reliability. Additionally, the limited number of high-quality within-cohort studies, exclusion of studies without age-stratified data, and inconsistent reporting of trio versus proband-only testing may affect generalizability. Funding for the study was provided by Illumina, Inc., and several authors disclosed employment or financial ties to the company. Publications by Kingsmore et al. (2019), discussed below, and Alfares et al. (2018), Bowling et al. (2017), Dimmock et al. (2021), French et al. (2019), Gubbels et al. (2020), Hu et al. (2020), Krantz et al. (2021), Retterer et al. (2016), Sanford et al. (2019), Stark et al. (2016), Sun et al. (2022), Tan et al. (2017), Trujillano et al. (2017), Vissers et al. (2017), and Wang et al. (2020), previously discussed in this policy, were included in the Pandey systematic literature review and meta-analysis.

A prospective cohort study by Wayhelova et al. (2024) evaluated the diagnostic utility of trio-based ES in 90 children from 85 families with unexplained severe neurodevelopmental disorders (NDDs) and/or multiple congenital abnormalities (MCAs). The intervention involved trio-based ES with a custom bioinformatics pipeline and variant prioritization algorithm. The study achieved a diagnostic yield of 48.9% (44/90), identifying 41 causative single-nucleotide variants or indels (45.6%) and 3 intragenic copy-number variants (CNVs) (3.3%). Of the 47 total causative variants, 53.2% were novel. De novo variants accounted for 51.2% of cases, and 15.6% were familial. Functional analysis using the PANTHER Gene Ontology system confirmed the involvement of affected genes in key developmental and molecular pathways. Potential threats to this study's validity include the relatively small cohort size and the lack of long-term clinical follow-up to assess the impact of diagnoses on patient outcomes. Additionally, while the study identified VUSs and candidate genes, their pathogenicity remains to be confirmed. The authors acknowledged that variant classification is dynamic and recommend periodic reanalysis but concluded that trio-based ES is an effective and reliable first-tier diagnostic test for children with unexplained NDDs, significantly improving diagnostic yield and enabling better clinical management and genetic counseling.

A multicenter, prospective cohort study by Zhang et al. (2024) examined the utility of trio-WES combined with copy number variant sequencing (CNV-seq) in young children diagnosed with global developmental delay (GDD). Conducted across six medical centers in China from July 2020 to August 2023, the study enrolled 434 children aged 12 to 60 months (60% male). Cognitive impairment, assessed using the Gesell scale, ranged from mild to profound (23% mild, 32% moderate, 28% severe, 17% profound). Common clinical phenotypes included craniofacial abnormalities (34%), hypotonia (21%), organ anomalies (14%), and skin abnormalities (11%). The combined use of trio-WES and CNV-seq resulted in a 61% diagnostic yield. Detection rates were highest among children aged 12-24 months, those with moderate to severe cognitive impairment, and those presenting with craniofacial abnormalities. Following bioinformatic analysis of identified genes, the authors suggested that genetic variants may influence brain development, contributing to cognitive impairment. The authors also found reinforcement of a previously reported association between the dopaminergic synapse and cognitive function. They concluded that combined trio-WES and CNV-seq is a valuable approach for elucidating the genetic basis of GDD and may enhance early diagnostic strategies. They recommended prioritizing genetic testing for children aged 12-24 months, those with moderate to profound cognitive impairment, craniofacial abnormalities, or complex phenotypes. Further research was advised in broader age groups and among individuals with diverse clinical presentations.

Mavura et al. (2024) assessed the diagnostic yield of ES across diverse genetic ancestries in a clinical cohort of 845 racially and ethnically diverse individuals, including pediatric and prenatal cases with suspected genetic disorders. Self-reported race/ethnicity was used, and Kolmogorov-Smirnov tests compared the distribution of estimated genetic ancestry among ES-positive, ES-negative, and inconclusive cases. Cochran-Armitage trend tests evaluated linear associations between diagnostic yield and genetic ancestry. No significant differences in diagnostic yield or the rate of inconclusive ES results were observed across ancestries (African, East Asian, European, Middle Eastern, Native American, Oceanian, South Asian). However, individuals of Middle Eastern and South Asian ancestry showed a higher prevalence of autosomal recessive homozygous inheritance, likely reflecting consanguinity. The authors advocated for equitable application of ES across all ancestries in the evaluation of undiagnosed genetic conditions.

A systematic review and meta-analysis by Gonzalez-Mantilla et al. (2023) evaluated the diagnostic yield of ES or GS in individuals with cerebral palsy (CP) to determine whether the diagnostic yield is comparable to that of other NDDs for which ES is recommended as a first-tier diagnostic test. The authors searched PubMed for studies published between 2013 and 2022 and included 13 studies comprising 2612 individuals with CP who underwent ES or GS. The pooled diagnostic yield was 31.1% (95% CI: 24.2%–38.6%), with higher yields in pediatric populations (34.8%) and in studies that applied exclusion criteria (e.g., pre-maturity, low birth weight, birth asphyxia) or neuroimaging findings (42.1%) compared to those that did not (20.7%). Among individuals with CP and comorbid intellectual disability/developmental delay (ID/DD),

the diagnostic yield was 37.8%, compared to 17.6% in those without ID/DD. Across five studies, 36.8% of individuals with pathogenic or likely pathogenic variants experienced changes in clinical management. The authors concluded that the diagnostic yield in CP is similar to that in other NDDs, supporting inclusion of CP in current recommendations for ES in the diagnostic evaluation of NDDs. However, the high heterogeneity across studies, particularly those without exclusion criteria or with inconsistent adherence to CP diagnostic criteria among the included studies, exclusion of VUSs, and lack of CNV calling or trio analysis in some included studies, may limit the reliability of these findings. A. publication by Moreno-De-Luca et al. (2021), previously discussed in this policy, was included in the Gonzalez-Mantilla systematic review.

Lowther et al. (2023) evaluated the diagnostic utility of short-read GS in individuals with autism spectrum disorder (ASD) and fetal structural anomalies (FSAs), comparing its performance to standard methods including karyotyping, CMA, and ES. The study included 6448 individuals representing 1612 ASD quartet families, 747 individuals representing 249 prenatal FSA trios, and 46 pre-selected singleton fetuses known to harbor clinically-reportable variants. All participants received GS alongside standard tests. GS identified diagnostic variants in 7.8% of ASD probands, nearly double the yield of CMA (4.3%) and almost triple that of ES (2.7%). When CNVs were systematically captured from the ES data, the ES yield increased to 7.4%. In unselected FSA cases, GS achieved an estimated diagnostic yield of 46.1%, representing increases of 17.2%, 14.1%, and 4.1% over karyotyping, CMA, and ES with CNV capture, respectively (36.1% increase over ES without CNV capture). Compared to the combined yield of all three standard tests, GS provided an incremental gain of 0.4% for ASD and 0.8% for FSAs. The authors suggested that these findings highlight the potential of GS to replace the conventional sequence of genetic tests, which detect only a limited subset of variants associated with ASD and FSAs. GS may also offer faster turnaround times, an important advantage in prenatal diagnostics. However, they cautioned that without advancements in variant annotation and interpretation, particularly in non-coding regions, GS is unlikely to significantly improve diagnostic yield for these conditions.

Chung et al. (2023) conducted a meta-analysis of 161 studies evaluating the diagnostic and clinical utility of ES and GS in adults and children with rare diseases. The analysis included 50,417 probands from 31 countries/regions over a 10-year period (2011-2021), representing diverse populations. Included studies reported diagnostic yield (defined as the proportion of individuals with a causative variant explaining their phenotype based on inheritance patterns, prior reports, and functional evidence) for both ES and GS. When available, data on clinical utility (i.e., changes in clinical management following diagnosis), VUS rates, novel gene discoveries, health economic outcomes, and diagnostic yield from ES reanalysis were also extracted and analyzed. The analysis of diagnostic utility demonstrated similar overall diagnostic yields for ES (0.38, 95% CI 0.36-0.40) and GS (0.34, 95% CI 0.30-0.38; p = 0.1). In a subgroup of 22 high-quality studies (per QUADAS-2), diagnostic rates remained comparable (ES: 0.43, 95% CI 0.35-0.51, 13 studies, n = 2612, I2 = 94%; GS: 0.34, 95% CI 0.28-0.41, 11 studies, n = 2170, I2 = 88%). Among nine studies directly comparing ES and GS (n = 2269), GS showed a non-significant 1.2-fold higher diagnostic odds (95% CI 0.79-1.83, p = 0.38). The analysis of novel gene discoveries and VUS indicated that GS studies reported a broader range of novel gene discoveries than ES studies (2-579 vs. 1-75 for ES), though the VUS rate did not differ significantly (p = 0.78). A subgroup comparison found children were 1.6 times more likely to receive a diagnosis than adults, regardless of sequencing method (95% CI 1.22-2.10, I2 = 0%, p < 0.01). ES reanalysis was compared to GS using the nine studies (n = 1748) that reported on ES reanalysis conducted one month to 3.4 years post-initial testing, in which additional diagnostic rates of 1%-16% over GS were reported. The pooled diagnostic yield from ES reanalysis (0.43, 95% CI 0.36-0.50; I2 = 89%) was significantly higher than that of GS (0.34, 95% CI 0.30-0.38; I2 = 95%), though further statistical comparison was limited by data availability. In the pooled meta-analysis of clinical utility, GS demonstrated higher clinical utility than ES (GS: 0.61, 95% CI 0.50-0.73, 16 studies, n = 3686, I2 = 94%; ES: 0.48, 95% CI 0.40-0.56, 47 studies, n = 8869, I2 = 97%). Among ten high-quality studies (n = 2170), GS also showed significantly greater clinical utility (0.77, 95% CI 0.64-0.90) compared to ES (0.44, 95% CI 0.30-0.58; p < 0.01). The authors suggested that these findings, along with increasing guidance on interpreting noncoding genomic variants, may support broader clinical adoption of GS.

Li et al. (2023) conducted a systematic review and meta-analysis to assess the diagnostic yield of ES and CMA in individuals with short stature. Twenty studies met inclusion criteria, comprising 1350 individuals tested with ES and 1070 with CMA. Eligible studies included at least ten participants diagnosed via ES or CMA. The analysis also examined diagnostic yield variations based on the use of ES as a first-tier versus last-resort test, as well as temporal trends using meta-regression. A genetic diagnosis was identified in a substantial proportion of participants. The overall diagnostic yield was 27.1% for ES (95% CI, 18.1%-37.2%) and 13.6% for CMA (95% CI, 9.2%-18.7%). No significant differences were observed in diagnostic yield over time or between first-tier (27.8%; 95% CI, 15.7%-41.8%) and last-resort ES testing (25.6%; 95% CI, 13.6%-39.6%) (p = 0.83). The researchers concluded that these findings underscore the diagnostic utility of ES and CMA in individuals with short stature, offering a valuable reference for clinicians. These results support informed decision-making regarding genetic testing strategies, potentially enabling more timely and accurate treatment.

Hayes conducted a Clinical Utility Evaluation (2023, updated 2024) on the use of genetic testing, including WES and WGS, in individuals with clinically diagnosed ASD. The review identified limited and low-quality evidence supporting the use of genetic testing in this population. While some evidence suggests that test results may inform further diagnostic and treatment decisions, there is insufficient evidence to demonstrate improved outcomes compared to standard evaluation protocols.

In its 2022 (updated 2024) Clinical Utility Evaluation, Hayes found insufficient evidence to support the use of WES or WGS for clinical decision-making or improving outcomes in adults with suspected neuromuscular or movement disorders. Very low-quality, limited evidence was identified for WES, highlighting the need for larger prospective studies to assess its impact on clinical management and outcomes. No studies were found evaluating WGS in this population, underscoring the need for research on its clinical utility.

Sánchez-Luquez et al. (2022) conducted a systematic review and meta-analysis to evaluate the molecular diagnostic yield of WES for intellectual disability (ID), assess the contribution of de novo mutations, and characterize associated genes. From studies published between 2010 and 2022, 37 articles were included. The overall diagnostic yield of WES was 42% (95% CI: 35–50%), with de novo mutations accounting for 11% (95% CI: 6–18%). Diagnostic rates were significantly higher when both biological parents or multiple affected family members were tested. The authors concluded that these findings support the utility of WES in diagnosing unexplained ID. Publications by Bowling et al. (2017) and Ewans et al. (2018), previously discussed in this policy, were included in the Sánchez-Luquez systematic review.

Lindstrand et al. (2022) conducted a retrospective analysis of individuals referred for diagnostic genetic testing at Karolinska University Hospital in Stockholm Sweden, focusing on those with ID and/or NDD. Three cohorts were evaluated. Cohort one (n = 100) underwent GS as a first-line test. Cohort two (n = 129) received GS as a second- or third-line test following inconclusive results from CMA and/or *FMR1* testing. Cohort three (n = 421) underwent CMA, with *FMR1* expansion testing performed in 50% of cases. Epilepsy and dysmorphic features were common across all cohorts. Diagnostic yield varied across cohorts: 35% in cohort one (GS as a first-line test), 26% in cohort two (GS as a secondary test), and 11% in cohort three (CMA/*FMR1* only). Notably, using GS as a secondary test delayed diagnosis by approximately one year. Additionally, among individuals with negative CMA/*FMR1* results (n = 338), no further genetic testing was pursued within 13 months, leaving them undiagnosed. The authors concluded that GS should replace CMA and *FMR1* testing as the first-line diagnostic approach for individuals with ID/NDD. However, the study's findings are limited by the lack of randomization and potential confounding factors.

Sheidley et al. (2022) conducted a systematic review and meta-analysis to evaluate the diagnostic yield of genetic tests commonly used in epilepsy, including GS, ES, multi-gene panels, and genome-wide comparative genomic hybridization (CGH)/CMA. The analysis included 154 studies encompassing 39,094 individual outcomes through 2020. An additional 43 publications were reviewed to assess non-diagnostic outcomes such as treatment modifications, prognostic insights, recurrence risk, and the role of genetic counseling. The overall diagnostic yield across all test types was 17%. GS had the highest yield at 48%, followed by ES at 24%, multi-gene panels at 19%, and CGH/CMA at 9%. Among phenotypic factors, only the presence of developmental and epileptic encephalopathy or neurodevelopmental comorbidities was significantly associated with higher diagnostic yield. Significant heterogeneity limited the analyses. Despite efforts to identify contributing variables, subgroup analyses did not meaningfully reduce heterogeneity, suggesting the presence of additional, unrecognized factors. While the study offers a comparative assessment of current genetic testing options, it also highlights the need for large, high-quality, prospective studies to explore variable interactions and assess the clinical utility of genetic evaluation in epilepsy.

Stranneheim et al. (2021) reported WGS results for 4437 individuals (3219 probands and 1218 relatives) tested at the Genomic Medicine Center Karolinska-Rare Diseases (GMCK-RD) since mid-2015. Of these, 84% underwent individual testing and 16% trio/family testing. A molecular diagnosis was achieved in 40% of cases, with diagnostic rates varying by disease group (19-54%). Frequently implicated genes included *COL2A1* (skeletal dysplasia), *SCN1A* (epilepsy) and *TNFRSF13B* (inborn errors of immunity). Negative cases contributed to further research, leading to the discovery of 17 novel disease-causing genes. Overall, WGS enabled diagnoses for over 1200 individuals with rare diseases. The authors emphasized the importance of continued clinical-academic collaboration to expand WGS access and improve diagnostic, prognostic, and therapeutic outcomes for individuals with rare diseases.

A Hayes Clinical Utility Evaluation (2021a, updated 2023) reported uncertain clinical utility for WES and insufficient clinical utility for WGS in guiding clinical decisions or improving outcomes in children (ages 18 years and younger) with undiagnosed neurological phenotypes following standard diagnostic testing. Among 12 WES studies, treatment changes and improved outcomes were observed in 2-22% of cases. For WGS, findings were limited to a small, narrowly defined infant population. The Hayes report emphasized the need for further research involving larger and more diverse pediatric cohorts with neurological symptoms.

An additional Clinical Utility Evaluation (Hayes, 2021b, updated 2024) found insufficient evidence supporting the use of WES or WGS to guide clinical care in individuals with a primary phenotype of ID alone. This evaluation did not address ID in the context of other conditions such as NDDs or GDDs. No peer-reviewed studies were identified that evaluated clinical utility specifically for individuals with isolated ID.

In a 2021 preliminary report, Smedley et al. presented findings from a pilot study on the role of GS in diagnosing rare diseases. The study involved 2183 families (4660 individuals) in the UK National Health Service who remained undiagnosed despite standard care, including cases where no diagnostic tests were available or existing tests excluded GS. Among the participants, 161 distinct rare disorders were represented across a wide range of disease categories, including cardiovascular, ciliopathy, dermatologic, congenital dysmorphic, endocrine, gastrointestinal, growth abnormality, hematologic/immunologic, auditory, metabolic, intellectual, neurologic, ophthalmologic, renal/urinary, respiratory, rheumatologic, skeletal, and neoplastic. Diagnostic yield was highest in families with larger pedigrees and in conditions likely to have a monogenic basis (35%) compared to those with complex etiologies (11%). Fourteen percent of diagnoses were achieved through a combination of automated analysis and research, particularly for cases involving noncoding, structural, or mitochondrial variants, or those poorly captured by ES. The study identified three novel disease genes and 19 new gene-disease associations. Notably, 25% of diagnoses had immediate clinical implications for affected individuals and their families. The researchers concluded that GS improved diagnostic yield for rare diseases and supported its use in diagnosing specific conditions. However, the study lacked a comparison group and its impact on clinical outcomes was supported only by anecdotal evidence presented in the publication.

Malinowski et al. (2020) conducted a systematic review to inform the development of an American College of Medical Genetics and Genomics (ACMG) evidence-based guideline on the use of ES and GS (Manickam et al., 2021). The review identified 167 primary studies reporting health, clinical, reproductive, and psychosocial outcomes of ES/GS in individuals with congenital anomalies, DD, or ID. Most studies were case reports or small series and all but one lacked a comparison group. Changes in clinical management or reproductive decision-making were the most commonly reported outcomes, noted in nearly all studies. The authors concluded that ES and GS potentially improve outcomes for both affected individuals and their families. However, the presence of conflicts of interest and unclear relevance to clinical outcomes warrant cautious interpretation. Publications by Cordoba et al. (2018), French et al. (2019), Petrikin et al. (2018), Powis et al. (2018), Stark et al. (2016), Stark et al. (2018), Tan et al. (2017), Tarailo-Graovac et al. (2016), and Vissers et al. (2017), previously discussed in this policy, were included in the Malinowski systematic review.

Srivastava et al. (2019) (included in Hayes 2021a and Hayes 2022), as part of the Neurodevelopmental Disorder Exome Scoping Review Work Group, conducted a scoping review and meta-analysis to compare the diagnostic yield of ES versus CMA in individuals with NDDs (defined as GDD, ID, and/or ASD). Analyzing 30 studies, they reported an overall ES yield of 36% (31% for isolated NDD and 53% for NDD with associated conditions), significantly higher than the 15-20% typically reported for CMA. The authors concluded that ES consistently outperforms CMA in evaluating unexplained NDDs and recommended ES as a first-tier diagnostic test. Limitations included a primary focus on ID and/or ASD, potentially excluding studies with less specific phenotypes. Additionally, some included studies lacked clear definitions for ASD or ID/GDD, and studies with heterogeneous cohorts or those involving mitochondrial DNA sequencing were excluded. Publications by Lee et al. (2014), Retterer et al. (2016), Tarailo-Graovac et al. (2016), and Vissers et al. (2017), previously discussed in this policy, were included in the Srivastava systematic review and meta-analysis.

Carss et al. (2017) evaluated the utility of WES and WGS in a cohort of 722 individuals with inherited retinal disease as part of the National Institute for Health and Care Research BioResource Rare Diseases study. Participants underwent WES (n = 72), WGS (n = 605), or both (n = 45). Diagnoses included retinitis pigmentosa (n = 311), retinal dystrophy (n = 101), cone-rod dystrophy (n = 53), Stargardt disease (n = 45), macular dystrophy (n = 37), and Usher syndrome (n = 37). Among the 117 individuals who underwent WES, pathogenic variants were identified in 59 cases (50%). Of the 45 individuals with negative WES results who subsequently received WGS, 14 additional pathogenic variants were detected. In three cases, the variants were located outside the WES capture regions; three involved large CNVs undetectable by WES; and three had low-quality WES data that failed to call the variants. In five cases, the variants were present in WES but required WGS to clarify inheritance patterns and rule out alternative diagnoses. Detection rates varied by phenotype, from 84% in Usher syndrome to 29% in cone-rod dystrophy. Ancestry also influenced diagnostic yield: 30% in individuals of African ancestry, compared to 55% in European and 57% in South Asian ancestry. Several factors may have influenced the findings of this study, including sequencing technology, phenotype screening, and the specific phenotypes included. The authors observed that individuals who had not undergone prior genetic screening exhibited a higher diagnostic yield, suggesting the cohort may have been enriched for more complex cases. This implies that WGS might achieve an even higher detection rate if used as a first line diagnostic tool. Additionally, the average target coverage for WES in this study was 43X, substantially lower than the > 80X median coverage typically recommended for clinical laboratories, which may have impacted the sensitivity of variant detection.

Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) - Use in Obstetrics

A prospective cohort study by Hadjipanteli et al. (2025) evaluated the diagnostic utility of trio-based WES in 33 families with second- or third-trimester pregnancy loss or abnormal prenatal ultrasound findings and unrevealing results from conventional genetic testing. Eligible cases included fetuses with abnormal sonographic findings or intrauterine death that had previously undergone karyotyping and array comparative genomic hybridization (array-CGH) with no causative findings. Among the 33 families, WES identified pathogenic or likely pathogenic variants in six families (18.18%) in genes associated with Mendelian disorders and consistent with the fetal phenotype and inheritance pattern. Two additional families had heterozygous variants in autosomal recessive genes potentially related to the phenotype, though a second pathogenic variant was not identified. Diagnosed cases primarily involved fetuses with multisystem (n = 4) or musculoskeletal (n = 2) anomalies. In total, 11 variants were identified across eight families. Eight variants were previously reported and three were novel. The study design incorporated variant validation by Sanger sequencing, contributing to the validity of the findings. However, limitations included incomplete phenotypic data, lack of autopsy in most cases, and the small sample size. The authors concluded that detailed and accurate prenatal phenotyping is critical to successful prenatal WES diagnoses.

A systematic review and meta-analysis by Jiang et al. (2025) evaluated the diagnostic utility of exome sequencing (ES) in fetuses with skeletal abnormalities who had normal karyotype or chromosomal microarray analysis (CMA) results. The investigators included 21 eligible studies comprising 476 fetuses with a mean gestational age of 24 weeks. The authors aimed to determine the additional detection rate of ES over traditional genetic testing methods and to assess how fetal phenotypes influenced diagnostic outcomes. The overall additional detection rate of ES was 63.2%. A total of 76 genes and 304 variant types were identified, with *FGFR3*, *COL1A1*, *COL1A2*, and *COL2A1* being the most frequently mutated. Subgroup analyses revealed higher detection rates in fetuses with abnormal ossification (85.0%), small thorax (81.5%), suspected long bone fractures or angulations (78.1%), and skull abnormalities (77.8%). A statistically significant difference ($p = 0.04$) in detection rate was observed between fetuses with short long bones and other skeletal abnormalities but without non-skeletal abnormalities (79.1%), and fetuses with short long bones plus skeletal and non-skeletal abnormalities (65.2%). Notably, this study demonstrates significant potential for publication bias. The authors suggest this may be due to the small cohort sizes and the inclusion of fetuses already evaluated as high-risk for a monogenic cause of their abnormalities after consultation with genetics specialists. The authors concluded that ES significantly improves the diagnostic yield for fetal skeletal abnormalities and should be integrated into clinical practice as a first-line test, particularly for cases presenting with classical skeletal dysplasia on ultrasound imaging. A publication by Deden et al. (2020), previously discussed in this policy, was included in the Jiang systematic review.

A systematic review and meta-analysis by Sotiriadis et al. (2025) evaluated the incremental diagnostic yield of prenatal ES in fetuses with an apparently normal phenotype and a normal karyotype or CMA. The study included four retrospective observational cohort studies comprising 1916 fetuses tested upon parental request following normal results on standard prenatal genetic testing. The pooled incremental yield of prenatal ES was found to be 1.6%, with most pathogenic or likely pathogenic variants being de novo and associated with autosomal dominant conditions. The incremental yield for a moderate or severe disease caused by de novo variants was 0.7%. All included studies were assessed as having low risk of bias. Trio analysis was used in most studies and all applied ACMG guidelines for variant classification. However, none of the studies confirmed normal phenotype postnatally or at the end of pregnancy and only one study reported variants of uncertain significance (VUSs). Secondary findings were inconsistently reported and definitions varied across studies. Further potential threats to validity include selection bias due to differing reasons for parental request for prenatal ES, the small number of included studies, and the limited sample size. Additionally, the absence of standardized classifications for disease severity limits interpretability. The authors conclude that more research is needed before incorporating prenatal ES into the clinical management of pregnancies without a medical indication for testing. A publication by Levy et al. (2025), previously discussed in this policy, was included in the Sotiriadis systematic review.

A systematic review and meta-analysis by Wang et al. (2025) evaluated the incremental diagnostic yield of prenatal ES in fetuses with skeletal abnormalities and negative results from CMA or karyotyping. The study included 26 observational studies comprising 524 fetuses with skeletal dysplasia or dysostosis identified by prenatal imaging. Trio sequencing was used in most studies. The pooled incremental diagnostic yield of ES was 60.2%. Subgroup analysis by phenotype showed the highest yield in fetuses with isolated skeletal dysplasia without non-skeletal system abnormalities (83.9%) and the lowest in isolated dysostoses (33.3%). The most frequently identified pathogenic variants were in *FGFR3* and collagen genes *COL1A1*, *COL1A2*, and *COL2A1*. Publication bias was not found to be significant, but potential threats to validity include heterogeneity in study populations, inconsistent use of phenotypic terminology, and differences in variant classification standards across studies. Some studies included highly selected cases, which may have inflated diagnostic yield. Additionally, incomplete reporting of postnatal outcomes and limited data on the impact of ES results on pregnancy decisions restrict generalizability. The authors concluded that ES can be beneficial to a personalized approach to clinical

consultation on prenatal skeletal system abnormalities. A publication by Deden et al. (2020), previously discussed in this policy, was included in the Wang systematic review.

A prospective study, systematic review, and meta-analysis by Blayney et al. (2024) evaluated the incremental diagnostic yield of prenatal ES over CMA or karyotype in fetuses with central nervous system (CNS) anomalies. The study included 30 eligible studies comprising 1583 cases. Eligible studies involved fetuses with CNS anomalies identified prenatally by ultrasound (with or without fetal MRI), where CMA or karyotype was non-diagnostic and prenatal ES was initiated based on phenotype. The primary outcome was the incremental diagnostic yield of prenatal ES. The pooled incremental yield of prenatal ES for any CNS anomaly was 32%, with 454 cases identified as having a pathogenic or likely pathogenic causative genetic variant. Subgroup analyses showed yields of 35% for CNS anomalies with multisystem involvement and 27% for isolated CNS anomalies. The incremental yield was 16% for single isolated CNS anomalies and 31% for multiple isolated CNS anomalies. Anatomical subtypes with the highest yields included posterior fossa anomalies (36%), midline anomalies (35%), and cortical anomalies (35%). The most common syndromes identified in isolated CNS anomalies were lissencephaly 3 (*TUBA1A*), Coffin-Siris syndrome (*ARID1A*/*B*), and congenital X-linked hydrocephalus (*L1CAM*). Findings suggest incomplete prenatal phenotyping may have occurred, as certain of the identified syndromes would typically present with multisystem involvement during imaging. The reported findings may also be affected by selection bias, which the authors attempted to minimize by setting an inclusion criterion requiring more than ten cases per study. Author disclosures include in-kind support from Illumina and one author is employed by Illumina. Publications by Chen et al. (2020), Deden et al. (2020), Fu et al. (2018), Gabriel et al. (2022), and Normand et al. (2018), previously discussed in this policy, were included in the Blayney systematic review.

A prospective cohort study by Luo et al. (2024) evaluated the diagnostic utility of WES in 149 fetuses with CNS abnormalities detected by prenatal ultrasound but with normal karyotyping and CMA results. All participants received care at a single tertiary prenatal diagnosis center between December 2016 and October 2022. WES was performed on fetal and parental DNA (trio WES). Pathogenic or likely pathogenic variants were identified and classified according to ACMG guidelines. The fetuses were categorized into three phenotypic groups: single and isolated CNS abnormalities (n = 69), multiple CNS abnormalities (n = 49), and CNS abnormalities with other organ system abnormalities (n = 31). The overall diagnostic yield of WES was 28.9% (43/149). Detection rates varied by phenotype: 17.4% (12/69) for single CNS abnormalities, 28.6% (14/49) for multiple CNS abnormalities, and 54.8% (17/31) for CNS abnormalities with other organ system abnormalities. The frequency of positive observations in the group with abnormalities in the CNS plus multiple organ systems compared to the two groups with isolated CNS abnormalities was determined to be statistically significant. The study found that WES identified a range of monogenic disorders and that 69.8% of pathogenic or likely pathogenic variants were de novo. The study design, which included standardized ultrasound protocols, trio-based sequencing, and variant confirmation by Sanger sequencing, supports the validity of the findings. Reliability was further enhanced by multidisciplinary review of VUSs. However, limitations include small sample sizes for specific abnormalities and the lack of functional validation for novel variants, forcing reliance on segregation analysis in family members. The authors concluded that WES can be a valuable diagnostic tool to inform prenatal diagnosis and facilitate genetic counseling when CNS abnormalities have been identified on imaging and karyotyping and CMA have been non-informative.

A systematic review and meta-analysis by Mustafa et al. (2024) evaluated the diagnostic yield of ES following negative CMA in cases of prenatally diagnosed agenesis of the corpus callosum (ACC). The study included 28 English-language studies published up to June 2022, encompassing 288 cases of prenatal ACC that underwent ES after negative CMA. A total of 116 pathogenic or likely pathogenic variants were identified across 83 genes. Of these initial 28 studies, the 15 studies reporting on at least three ACC cases (totaling 268 cases) were included in the meta-analysis. Trio ES was performed in most cases (95.6%). Duo ES was performed in one case and proband-only ES was performed in four cases. The primary outcome was the proportion of cases with pathogenic or likely pathogenic variants identified by ES. The pooled diagnostic yield was 43%. Subgroup analysis showed the highest yield in ACC with extracranial anomalies (55%) followed by ACC with other cranial anomalies (43%) and isolated ACC (32%). Limitations of this analysis included high heterogeneity among studies, lack of consistent reporting on whether ACC was complete or partial, and potential misclassification of phenotypes, which were based on imaging findings that may not have detected the full spectrum of anomalies. There was also an absence of postnatal confirmation in some cases. Additionally, the use of different sequencing platforms and inclusion of both preselected and unselected cohorts may have influenced diagnostic yield. The authors determined that their findings support the use of ES in prenatal ACC cases, including isolated presentations, after negative CMA results, due to a substantial incremental diagnostic yield. Publications by Aarabi et al. (2018), Deden et al. (2020), Fu et al. (2018), Lord et al. (2019), Normand et al. (2018), and Petrovski et al. (2019), previously discussed in this policy, were included in the Mustafa systematic review.

A systematic review and meta-analysis by Reilly et al. (2024) evaluated the incremental diagnostic yield of prenatal ES over CMA and/or karyotype in fetuses with congenital heart defects (CHDs). The study included 21 eligible studies comprising 1957 fetuses with a prenatally diagnosed CHD and negative results from standard genetic testing. The primary

objective was to assess the added diagnostic value of prenatal ES in isolated CHD, in CHD with extra-cardiac malformations, and across anatomical CHD subtypes. The overall incremental yield of prenatal ES over standard testing was found to be 17.4% for all CHDs, 9.3% for isolated CHD, and 35.9% for CHD associated with extra-cardiac malformations. The highest yield was observed in the complex lesions/heterotaxy subgroup at 35.2%. The most frequently identified syndromes were Kabuki syndrome and Noonan syndrome. Over half of the pathogenic variants identified were de novo variants identified in autosomal dominant disease genes. The authors suggest that prenatal ES may have clinical utility in the evaluation of some isolated cardiac lesions, but there is a high likelihood of monogenic etiology when the fetus presents with both CHD and extra-cardiac malformations. Limitations of this study include high heterogeneity among studies, high risk for publication bias determined by funnel plot evaluation, potential selection bias due to low uptake of invasive testing in isolated CHD, and incomplete phenotypic data due to the prenatal setting. Additionally, the inability to isolate the incremental yield for complex and heterotaxy subgroups due to small sample sizes was noted. One author discloses employment by Illumina. Publications by Fu et al. (2018), Lord et al., (2019), Normand et al, (2018), and Petrovski et al. (2019), previously discussed in this policy, were included in the Reilly systematic review.

A systematic review, prospective cohort study, and meta-analysis by Sonner et al. (2024) evaluated the incremental diagnostic yield of prenatal ES over CMA and/or karyotyping in fetuses with congenital anomalies of the kidney and urinary tract (CAKUT). The study included 14 studies (409 cases) published between January 2010 and February 2023, along with two additional cohorts, one from the Prenatal Assessment of Genomes and Exomes (PAGE) study and another from the NHS England Genomic Laboratory Hub. Eligible studies had at least five CAKUT cases identified by ultrasound which had negative CMA or karyotype results preceding prenatal ES. CAKUT was classified as isolated or multisystem, and further subtyped, with isolated bilateral echogenic kidneys (BEKs) as the only isolated CAKUT subgroup that could be analyzed separately due to the small size of all other cohorts. The pooled incremental diagnostic yield of prenatal ES was 26% across all cases, with the highest yields in cases with multisystem anomalies (32%) and BEKs (51%). In contrast, the yield for isolated CAKUT excluding BEKs was modest at 8%. The most frequently identified pathogenic variants were in genes associated with Bardet-Biedl syndrome, the polycystic kidney diseases (*PKD1*, *PKD2*, *PKHD1*), and renal cysts and diabetes syndrome (*HNF1B*). The study concludes that the high incremental yield in BEKs and multisystem CAKUT supports the substantial diagnostic benefit of prenatal ES in cases of BEKs or multisystem CAKUT, and that this supports its targeted use in prenatal care, especially in resource-limited settings. Limitations include high heterogeneity of included studies and selection bias within all studies, small sample sizes in most subgroups, and lack of a universal classification system for CAKUT. Publications by Chen et al. (2020), Lord et al. (2019), and Petrovski et al. (2019), previously discussed in this policy, were included in the Sonner systematic review.

A retrospective case series by Xiang et al. (2024) evaluated the diagnostic utility of single, trio, and quad WES with exome-based copy number variant (CNV) analysis as an initial testing strategy for pregnancy loss. Study participants were 375 families who experienced pregnancy loss or termination due to fetal structural anomalies referred to a single genetic reproductive medicine clinic affiliated with an academic medical center between November 2019 and January 2024. Inclusion criteria encompassed miscarriage before 20 weeks gestational age, stillbirth at or after 20 weeks, and termination due to fetal structural anomalies identified by prenatal ultrasound. The overall detection rate was 32.3% (121/375), including aneuploidy and triploidy (7.5%, 28/375), CNVs (5.1%, 19/375) and single nucleotide variants (SNVs)/indels (19.7%, 74/375). Among these, 27.5% (103/375) were classified as pathogenic or likely pathogenic and an additional 4.8% (18/375) had VUSs with potential clinical relevance. The highest diagnostic yield was observed in cases with increased nuchal translucency (63.6%, 7/11) and skeletal anomalies (63.3%, 19/30). A higher diagnostic yield was observed in the families with two fetuses in which quad WES was performed (55.6%), compared to both the single WES (32.5%) and the trio WES (31.5%) subgroups. De novo mutations were identified in 36 of the 74 cases with SNVs/Indels, including 33 autosomal dominant and three X-linked variants, highlighting their significant contribution to the genetic etiology of fetal anomalies. Validation methods included Sanger sequencing, qPCR, and RNA analysis. The study design incorporated rigorous variant interpretation, confirmation of CNVs and splicing effects, and use of standardized classification criteria, supporting the validity and reliability of the findings. However, limitations include the retrospective design, selection bias toward terminated pregnancies, and limited prenatal phenotypic data due to reliance on ultrasound. The authors recommended implementing WES in clinical practice as a first-line test for pregnancy loss and fetal structural anomalies to improve diagnostic yield and inform recurrence risk counseling. The findings need to be reproduced before becoming standard practice and may not be generalizable to the US population.

Diderich et al. (2024) conducted a retrospective analysis of ES results from 629 fetuses with isolated or multiple ultrasound-detected anomalies to evaluate its diagnostic yield in a prenatal setting. ES was followed by testing with a large multi-gene panel (~3400 genes) associated with congenital anomalies and/or intellectual disability. Variant analysis included trio-based filtering for de novo, compound heterozygous, homozygous, X-linked, imprinted gene, and known pathogenic variants. Pathogenic or likely pathogenic variants were identified in 14% of cases (88/629, 95% CI 11.5%–16.9%).The likelihood of diagnosing a monogenic disorder ranged from approximately one in nine (49/424) for cases with

a single major anomaly to one in five (32/147) for those with multisystem anomalies. The authors concluded that these findings support the use of ES not only in cases with multiple anomalies but also in those with isolated anomalies.

In a 2023 systematic review and meta-analysis, Shreeve et al. evaluated the incremental diagnostic yield of WGS compared to WES and/or CMA in fetuses and infants with anomalies detectable or potentially detectable via prenatal ultrasound. Secondary outcomes included turnaround time and DNA quantity requirements. The review included 18 studies encompassing 1284 cases: eight prenatal cohorts (754 cases) and ten postmortem, neonatal, or infant cohorts with congenital structural abnormalities. WGS demonstrated a non-significant incremental yield of 1% over WES (95% CI 0%-4%, I2 = 47%). In contrast, WGS showed a significant incremental yield over QF-PCR/CMA: 26% overall (95% CI 18-36%, I2 = 86%), 16% in prenatal cases (9-24%, I2 = 85%), and 39% in postnatal cases (95%CI 27-51%, I2 = 53%). The pooled median turnaround time for WGS was 18 days. However, only one study reported turnaround time for CMA/WES, precluding comparison. Overall, WGS significantly improved diagnostic\ yield compared to CMA but not compared to WES. The authors concluded that current evidence is insufficient to support routine use of WGS over CMA or WES. However, WGS may offer advantages in requiring less DNA and enabling faster turnaround times. Further research is recommended to validate these potential benefits. Publications by French et al. (2019), Mestek-Boukhibar et al. (2018), and Petrikin et al. (2018), previously discussed in this policy, were included in the Shreeve systematic review and meta-analysis.

Miceikaite et al. (2023) reported a 25% increase in diagnostic yield using trio WES and WGS compared to standard CMA in pregnancies with negative CMA results. The study included 40 pregnancies between 12- and 21-weeks gestation, all presenting with fetal anomalies or increased nuchal translucency (≥ 5 mm). Each case underwent both trio WES/WGS and CMA. Of the 40 pregnancies, 16 (40%) had a genetic sequence variant, CNV, or aneuploidy consistent with the fetal phenotype. All six chromosomal abnormalities detected by CMA were also identified by WES/WGS. WES demonstrated greater consistency than WGS in detecting mosaicism, likely due to its deeper sequencing capacity. The researchers asserted that although this study is limited by small sample size, the results bolster existing evidence of the higher diagnostic yield of WES/WGS over CMA and speculated that WES/WGS has promise as a standalone prenatal diagnostic test.

Mellis et al. (2022) conducted a systematic review and meta-analysis to assess the diagnostic yield of ES for prenatal evaluation of fetal structural anomalies following a normal CMA result. The authors assessed 148 articles and included 72 reports from 66 studies in this review, representing a total of 4350 fetuses. Incremental diagnostic yield of ES over CMA and karyotyping was evaluated through meta-analysis, with additional analyses examining the influence of case selection and fetal phenotype on diagnostic yield. The pooled incremental diagnostic yield of ES was 31% (95% CI 26%-36%, $p < 0.0001$), with significant variation across phenotypic subgroups, ranging from 2% for isolated increased nuchal translucency to 53% for isolated skeletal abnormalities. Pre-selected cases with a high likelihood of monogenic etiology demonstrated a significantly higher diagnostic yield compared to unselected cases (42% vs 15%, $p < 0.0001$). These findings support the conclusion that prenatal ES can identify a diagnosis in an additional 31% of fetuses with structural anomalies following nondiagnostic CMA and karyotyping. Diagnostic yield varies by affected body system and may be enhanced through targeted case selection following multidisciplinary review suggesting a monogenic etiology. This review was limited by substantial heterogeneity among the included studies, along with variability in sample sizes and analytical methods, all of which likely influenced diagnostic yield. The authors emphasized the need for continued research to better understand the clinical utility of prenatal ES; specifically, to identify which pregnancies are most likely to benefit, how to prioritize cases for testing, and how to address challenges in interpreting variants when phenotypic information is incomplete or non-specific. Publications by Aarabi et al. (2018), Chen et al. (2020), Deden et al. (2020), Fu et al. (2018), Lord et al. (2019), Normand et al. (2018), and Petrovski et al. (2019), previously discussed in this policy, were included in the Mellis systematic review.

To explore the role of ES in cases of multisystem anomalies, Pauta et al. (2022) conducted a systematic review to determine its incremental diagnostic yield in fetuses presenting with structural anomalies in at least two different anatomical systems and normal CMA or karyotyping results. Seventeen studies met inclusion criteria, providing data for 694 fetuses. Subgroup analysis compared the diagnostic yield of the solo approach (testing the fetus alone) and the trio approach (testing the fetus along with both biological parents). Pathogenic or likely pathogenic variants were identified in 213 fetuses, corresponding to an incremental diagnostic yield of 33% (95% CI, 27-40%) for ES, with comparable diagnostic yields for the solo approach (30%) and the trio approach (35%). Based on their findings, the authors concluded that ES can identify potentially causative genetic variants in approximately one-third of cases where CMA or karyotyping was non-diagnostic, with no meaningful difference between the solo and trio approaches.

In a 2021 systematic review and meta-analysis, Pauta et al. evaluated the diagnostic yield of ES in pregnancies with similar, recurrent fetal structural anomalies, normal microarray results, and no identified familial disease. They identified nine studies encompassing 140 such cases. Pathogenic or likely pathogenic variants were identified in 57 fetuses,

yielding an incremental diagnostic rate of 40% for ES (95% CI: 26% to 54%). Most identified conditions (86%) followed a recessive inheritance pattern, with 42% of these variants being homozygous. Higher diagnostic yields were observed in cases involving multisystem anomalies, which accounted for over half of the positive results. The authors concluded that ES is a valuable tool for identifying the etiology of recurrent fetal malformations, particularly in monogenic syndromes, and anticipated a transition toward genome sequencing in the near future.

A 2020 (updated 2023) Hayes Clinical Utility Evaluation found insufficient evidence that fetal WES and WGS improve the diagnostic rate or guide prenatal and postnatal management when abnormalities are detected by ultrasound or other testing. The report emphasized the need for large-scale studies including outcomes data and clinical impact to establish their utility in the prenatal setting.

Reanalysis of WES and WGS Data

A retrospective case series by Vorsteveld et al. (2024) evaluated the diagnostic yield of clinical exome sequencing (ES) and the added value of systematic reanalysis in a single-center cohort of 1300 participants with suspected inborn errors of immunity (IEI). The study population included both pediatric and adult participants referred to Radboud University Medical Center between 2013 and 2021. Standard ES was performed using in-silico IEI gene panels, and reanalysis was conducted at a median interval of 47.5 months using an updated gene panel, improved variant annotation, and copy number variant (CNV) detection. After initial ES, a molecular diagnosis was established in 154 participants (11.8%). Systematic reanalysis identified additional relevant variants in 60 of 1146 previously undiagnosed participants (5.2%), resulting in 24 participants receiving new conclusive diagnoses (2.1%) and 22 participants with newly-identified candidate variants (1.9%). This increased the overall diagnostic yield to 15.2%. Most new findings were attributed to newly described IEI genes, variant reinterpretation based on updated literature and databases, novel mutational mechanisms, or CNV detection. Among participants with a new diagnosis after reanalysis, 83.3% had actionable findings with potential implications for clinical management. The study design included expert multidisciplinary review of all variants, use of established variant classification guidelines, and integration of phenotype-genotype correlations, which support the validity of the findings. Limitations include the retrospective design, potential underrepresentation of certain IEI subtypes, limited exome-wide analysis in some participants, and lack of longitudinal clinical outcome data to assess the impact of reanalysis on patient care. Overall, the findings supported the clinical utility of periodic ES reanalysis in IEI.

A retrospective cohort study by Wilke et al. (2024) evaluated 100 patients with single-system diseases from the Mayo Clinic's Program for Rare and Undiagnosed Diseases (PRaUD) who had nondiagnostic results from custom exome- or genome-based targeted panels (EGBP), to determine whether reanalysis of raw ES or genome sequencing (GS) data could improve diagnostic yield. The cohort included 80 participants with ES data and 20 with GS data, with a mean age of 43 years. Most participants had renal (n = 44) or auto-inflammatory (n = 29) phenotypes. Reanalysis identified additional diagnostic findings in four of 100 cases. The study concluded that ES and GS offer diagnostic yields comparable to targeted EGBP in single-system diseases but emphasized that EGBP may miss diagnoses due to evolving gene-disease associations, highlighting the importance of periodic updates and reanalysis to capture newly described gene-disease associations. However, potential threats to this study's reliability include its small sample size, the use of convenience sampling which may introduce selection bias, and the reliance on retrospective data.

The Undiagnosed Rare Disease Program of Catalonia (URD-Cat) (Bullich et al., 2022) conducted a systematic reanalysis of genomic panel, ES, and GS data, along with standardized phenotypes, from 543 individuals in 323 families with undiagnosed neurological disorders. The study evaluated relatedness, consanguinity, runs of homozygosity, single nucleotide variants, indels, and CNVs, using a customized Genome-Phenome Analysis Platform (GPAP) for collaborative interpretation. Reanalysis led to diagnoses in 20.7% of individuals, including 1.8% diagnosed through additional genomic data that revealed a second pathogenic heterozygous variant. The study demonstrated a significantly higher diagnostic yield from family-based ES and GS reanalysis compared to individual panels. Most new diagnoses (50.8%) were attributed to recently established gene-disease associations, with additional/improved bioinformatic analyses (19.7%) and standardized phenotyping (18%) also contributing. Reanalysis resulted in diagnoses for 67 individuals. According to their referring clinicians, these diagnoses were expected to improve clinical management, enable genetic counseling for patients and relatives, and potentially facilitate diagnoses in other affected family members. The authors concluded that the GPAP tool was instrumental in enabling efficient genomic reanalysis and data sharing.

Schobers et al. (2022) evaluated the effectiveness of various strategies for reanalyzing negative ES results in children with undiagnosed neurological conditions. The study involved 103 children who underwent exome resequencing five years after initial negative results. It also assessed the frequency of physician-initiated routine reevaluations. Of the 103 individuals, physicians requested a reevaluation for 45, resulting in 18 diagnoses (31% diagnostic yield). Systematic reevaluation identified an additional 14 diagnoses, increasing the total diagnostic yield to 53%. These new findings were attributed to enhanced bioinformatics, improved sequencing coverage, variant reclassification, and novel gene-disease associations. Notably, 11 of the 14 diagnoses from systematic reevaluation were in individuals who had not recontacted

their referring physician. The authors concluded that both resequencing and reanalysis of existing ES data are effective in identifying additional genetic diagnoses. The findings highlight that without systematic reanalysis, many affected individuals may miss timely diagnoses.

Tan et al. (2020) conducted a systematic reanalysis of ES data for 58 previously undiagnosed individuals, complemented by a literature review of similar studies. The first reanalysis, performed four to 13 months after initial results, included genes newly associated with disease. A second reanalysis at nine to 18 months considered all disease-related genes. At 25-34 months, all cases were reviewed to compare diagnostic strategies. Reanalysis of existing ES data at two points in time did not yield new diagnoses. However, incorporating additional methods, such as repeat sequencing, trio sequencing, and microarray-based CNV detection, resulted in ten new diagnoses (17%) within the cohort. The literature review identified 27 peer-reviewed studies, with a median diagnostic yield of 15% and median reanalysis interval of 22 months. Based on their findings, the researchers recommended a reanalysis interval of at least 18 months, incorporating diverse diagnostic strategies for individuals who remain undiagnosed after initial ES.

Rapid Whole Exome Sequencing (rWES), Rapid Whole Genome Sequencing (rWGS), and Ultra-Rapid Whole Genome Sequencing (urWGS)

Genomic sequencing tests with rapid turnaround-times have been developed for use in critically ill children in the inpatient setting. Current peer-reviewed evidence supporting the clinical utility of rWES, rWGS, and urWGS in the outpatient setting is lacking and their use is not supported at this time.

Xiao et al. (2022) conducted a systematic review and meta-analysis of 23 studies involving 1567 critically ill infants to assess the diagnostic utility of rWES and rWGS. The pooled diagnostic yield of rapid sequencing was 42% (95% CI: 0.37-0.49, $I^2 = 79\%$, $p < 0.1$). rWES demonstrated a slightly higher diagnostic rate of 50% (95% CI: 0.41-0.61; $I^2 = 74\%$; $p < 0.01$), compared to 37% for rWGS (95% CI: 0.30-0.46; $I^2 = 77\%$; $p < 0.01$). The authors concluded that their findings support the use of rWES and rWGS in the evaluation of critically ill infants. However, they emphasized the need for additional large-scale, high quality, randomized controlled trials to address limitations in the existing evidence base. Given that all included participants were critically ill, the generalizability of these results to outpatient or less acute settings remains uncertain. Publications by Kingsmore et al. (2019), discussed below, and Dimmock et al. (2021), Gubbels et al. (2020), French et al. (2019), Mestek-Boukhibar et al. (2018), Petrikin et al. (2018), Stark et al. (2018), and Wang et al. (2020), previously discussed in this policy, were included in the Xiao systematic review and meta-analysis.

Kingsmore et al. (2019) reported on the NSIGHT2 prospective, randomized, controlled, and blinded trial at Rady Children's Hospital evaluating the clinical utility of rWES and rWGS in 1248 critically ill infants. Of these, 46% had conditions of unknown etiology and parent-child trio samples were available for 69% of families. Within 96 hours of admission, 213 infants (17%) were enrolled. Due to disease severity, 24 infants (11%) received urWGS and were not randomized. The remaining 189 infants were randomized to rWES (n = 95) or rWGS (n = 94). rWGS demonstrated superior analytical performance compared to rWES, particularly in identifying ClinVar pathogenic variants ($p = 0.0001$). Diagnostic yields were comparable between rWGS and rWES (19% vs. 20%), with no significant difference in time to diagnosis (11.0 vs. 11.2 days). urWGS achieved a higher diagnostic rate (46%) than rWES/rWGS ($p = 0.004$) and delivered results more quickly ($p < 0.0001$). Reflex trio testing following a negative proband result increased diagnostic yield by 0.7%. The authors concluded that rWES and rWGS are suitable as first-tier diagnostic tests for critically ill hospitalized infants. urWGS offered the fastest turnaround time, which was particularly valuable for cases requiring immediate clinical intervention. However, since all participants were seriously ill, the applicability of these findings to less severe or outpatient populations remains uncertain. The authors recommended further studies directly comparing urWGS and rWES, ideally using larger cohorts and applying both tests to each proband.

Whole Transcriptome Sequencing

There is insufficient evidence to support the use of whole transcriptome sequencing in the diagnosis or management of constitutional genetic disorders at this time. Existing evidence is limited by small sample sizes, tissue-specific gene expression, and concerns about generalizability. The clinical utility of this technology has not been demonstrated.

In a prospective case series, Rozevska et al. (2025) evaluated the diagnostic utility of combined genome sequencing (GS) and transcriptome sequencing (TS) in 37 participants with suspected inborn errors of immunity (IEI), primarily common variable immunodeficiency (CVID) and predominantly antibody deficiency (PAD), with no prior genetic testing. The study identified a genetic diagnosis in 14% (5/37) of cases, including pathogenic variants in *STAT1*, *ADA2*, *SH2D1A*, *NRAS*, and *NR2F1*. TS was instrumental in characterizing a complex structural variant in *SH2D1A* and in interpreting variant effects, although standard TS analysis pipelines showed limitations in sensitivity, failing to detect several known splicing or expression abnormalities. GS and TS led to diagnostic reclassification in three cases initially diagnosed with CVID/PAD, including identification of RAS-associated autoimmune leukoproliferative disorder and ADA2 deficiency. While

the combined approach provided these critical insights in complex or ambiguous genomic variants, the overall improvement in diagnostic yield over exome sequencing was limited and most of the identified variants could also have been detected by exome sequencing, supporting the use of GS and TS as second-tier tests in unresolved IEI cases. The authors noted that TS is limited by tissue-specific expression and that some IEI-associated genes are insufficiently expressed in blood to be analyzable, particularly in complement deficiencies.

Lee et al. (2020) investigated the utility of transcriptome sequencing (RNAseq) in enhancing diagnostic yield from whole exome sequencing (WES) or whole genome sequencing (WGS) in 113 probands with suspected rare genetic disorders. All participants underwent comprehensive clinical evaluations without receiving a diagnosis and were subsequently referred to the Undiagnosed Diseases Network (UDN). RNAseq was performed alongside WES or WGS to support genome-wide variant interpretation. WES was performed on 29 individuals and WGS on 77, with previously obtained data from seven individuals reanalyzed. Following clinical evaluation by the UDN, 13 individuals were excluded due to inconsistent clinical information. Of the remaining 100 probands, 31 received a diagnosis based on WES or WGS alone. Forty-eight families (91 samples) with negative WGS results for coding single nucleotide variants, small indels, and structural variants underwent RNA sequencing (RNAseq), alongside 284 control samples. Integration of RNAseq with WGS data led to seven additional diagnoses (15%; 95% CI, 7–27%), increasing the overall diagnostic yield to 38% (95% CI, 29–48%). Notably, the variants identified in these seven cases would not have been detected without RNAseq. The study's limitations include a small cohort evaluated at a highly specialized referral center and challenges in detecting relevant genes due to limited expression in accessible tissues. Broader population studies and advancements in differentiating accessible cells into specific cell types are recommended to enhance RNAseq-based gene detection.

Optical Genome Mapping (OGM)

There is currently insufficient evidence to support the use of (OGM) for any indication. Although it shows early promise for comprehensive detection of chromosomal abnormalities, further technological development and additional studies are needed to demonstrate clinical utility.

Mantere et al. (2021) conducted a proof-of-principle study evaluating OGM for detecting constitutional chromosomal abnormalities. Ultra-high-molecular-weight DNA was extracted from 85 blood or cultured cell samples and analyzed using OGM. Referral indications included developmental delay with or without congenital malformations (n = 49), reproductive disorders (n = 15), family history of chromosomal abnormalities (n = 2), and abnormal prenatal screening or ultrasound findings (n = 9). OGM results were compared to established diagnostic methods, including karyotyping, FISH, and copy number variant microarray. OGM demonstrated 100% concordance with standard assays across 99 chromosomal abnormalities involving non-centromeric breakpoints. According to the authors, these findings suggest that OGM can detect nearly all chromosomal abnormality types. They anticipated continued advancements in OGM's technical and analytical capabilities, supported by progress in completing the human reference genome. Improvements in structural variant and CNV reporting algorithms, as well as faster turnaround times, are expected. These developments will enable large-scale, high-quality clinical utility studies, which are essential for OGM's integration into diagnostic workflows.

Additional peer-reviewed literature on OGM comprises case reports or small case series evaluating its application across various clinical indications (Dremsek et al., 2021; Dai et al., 2022; Erbe et al., 2023; Ke et al., 2023; Zhang et al., 2023).

Epigenetic Signature Analysis

There is currently insufficient evidence to support the use of epigenetic signature analysis in the diagnosis or management of constitutional disorders. Additional studies are needed to demonstrate clinical utility.

In a retrospective case series by Kerkhof et al. (2024), the diagnostic utility of clinical DNA methylation episignature testing was evaluated in 2399 participants with suspected rare genetic disorders referred to the international EpiSign Clinical Testing Network between May 2019 and January 2023. The cohort included 1667 cases undergoing comprehensive analysis of validated episignatures, imprinting, and promoter regions, yielding a diagnostic rate of 18.7% (312/1667), and 732 cases undergoing targeted analysis for variants of uncertain significance or suspected diagnoses without molecular confirmation, with a diagnostic yield of 32.4% (237/732). The EpiSign assay employed a support vector machine–based classification algorithm and hierarchical clustering to compare participant methylation profiles against a reference database. Positive results required concordance in at least two of three analytic parameters. Confirmation testing in a subset of positive cases without prior molecular findings identified causative variants in 58.1% of high-confidence and 23.1% of moderate-confidence episignature-positive cases. However, the authors noted some key limitations of episignature analysis: it is currently restricted to conditions with known biomarkers and has the potential to return false positive results in cases of overlapping episignatures from functionally related but uncharacterized genes. The study concluded that episignature testing provides significant diagnostic yield and clinical utility, particularly in genetically

unresolved cases, and proposed standardized interpretation and reporting guidelines to support clinical implementation. This study's principal investigator is a shareholder in EpiSign Inc., which commercializes the EpiSign technology.

Clinical Practice Guidelines

American Academy of Neurology (AAN)/American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)

The AAN and AANEM have indicated that there is low level evidence to consider whole exome sequencing (WES) or whole genome sequencing (WGS) in selected individuals with congenital muscular dystrophy (CMD) in whom a genetic variant has not been identified through standard testing approaches. Individuals with CMD that do not have causative genetic variations identified through routine methods can be considered for WES or WGS when those technologies are clinically available. Evidence Level C (Kang et al., 2015, reaffirmed 2024).

American Academy of Pediatrics (AAP)

Rodan et al. (2025) reported the AAP recommendations for the genetic evaluation of global developmental delay/intellectual disability (GDD/ID), basing the recommendations on diagnostic yield and practical considerations for the general pediatrician such as test complexity and impact on management. The AAP continues to recommend chromosome microarray (CMA) in the first-tier agnostic evaluation for GDD/ID along with WES (sequential or concurrent). Depending on the situation, testing additional affected or unaffected family members for further segregation data may be useful. If WGS is initially performed, there is typically adequate evaluation of copy number variants (CNVs), so CMA can be deferred in most cases. If negative, WES/WGS may be clinically reanalyzed every one to two years following the initial test. Genome-wide methylation signature testing has become clinically available, although it is still only able to evaluate for a relatively small number of disorders, limiting its utility primarily to the evaluation of variants of uncertain significance (VUSs) in these genes or as a screening evaluation following otherwise nondiagnostic testing.

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)

In an AANEM 2016 consensus statement, the group stated that while they do not endorse or recommend a specific testing methodology, genetic testing to establish a molecular diagnosis is a crucial step in providing optimal care to individuals with neuromuscular disorders (Kassardjian et al., 2016, reaffirmed 2021).

American College of Medical Genetics and Genomics (ACMG)

In 2023, ACMG (Raca et al., 2023) published guidance in a "points to consider" document for clinical laboratory geneticists and other clinicians advising on the detection of germline structural variants using WES or WGS. Their recommendations include the following:

- Test selection should be based on the clinical phenotype, medical and family history, results of ancillary testing, and scope of the differential diagnosis. If the clinician suspects a particular disorder or if a patient presents with a phenotype known to be commonly caused by a specific set of genes, a targeted test may be more appropriate than a genome-wide assay.
- Non-specific or overlapping presentations may call for broader testing strategies such as CMA or WES/WGS.
- Parental samples should be pursued whenever feasible at the direction of the clinical laboratory; note that some laboratories/assays require parental samples to be sent in conjunction with the proband samples and others will make requests on a case-by-case basis at the time of resulting. Diagnostic yield has been shown to be higher when analyzing a trio as compared to proband-only WES.
- In the prenatal setting, for a fetus with imaging abnormalities and/or abnormal noninvasive prenatal screening, standard CMA and karyotyping should be considered. If negative, fetal WES or WGS may be considered.
- At present, there is no data supporting the clinical use of WES/WGS for other reproductive indications, such as the identification of sonographic markers suggestive of aneuploidy or a history of recurrent unexplained pregnancy loss.
- Postnatal reanalysis should be considered if the initial prenatal test was nondiagnostic.

An ACMG Practice Resource (Li et al., 2022) addressed the clinical evaluation and diagnosis of hearing loss, stating that due to a high likelihood of genetic etiology in infants and children with hearing loss, a clinical genetics evaluation, including counseling, should be a standard part of care for any child with confirmed hearing loss. If, after comprehensive evaluation including physical examination, medical and birth history, three-generation pedigree, and family medical history, findings suggest a syndromic genetic etiology for hearing loss, genetic counseling and testing should be provided. This may include single-gene tests, hearing loss multi-gene panels, WES, WGS, chromosome analysis, or microarray- or next-generation sequencing (NGS)- based CNV analysis, depending on the clinical findings. If findings do not suggest a known syndrome, a tiered approach using a comprehensive hearing loss genetic panel followed by genome-wide testing such as WES or WGS, if initial testing is negative, may be considered. Ordering providers must have awareness of the specific genes included in the chosen panel (to ensure the panel includes the most appropriate and applicable genes) as

well as the performance of the testing platform chosen. Testing of the mitochondrial genome including deletion analysis for syndromic mitochondrial disorders is appropriate in certain specific settings. If any/all genetic testing performed does not reveal an etiology for the individual's hearing loss, the possibility of genetic etiology remains and further testing could potentially be pursued in a research setting.

In a 2021 practice guideline authored by Manickam et al., the ACMG asserted their position that evidenced-based literature supports clinical utility of WES and WGS on both active and long-term management of individuals with congenital anomalies, developmental delay (DD), and/or ID. Based on their comprehensive systematic review, limited evidence for negative outcomes was found. As such, the ACMG recommends use of WES and WGS as a first- or second-tier test for individuals with one or more congenital anomalies with onset prior to one year of age or for individuals with DD/ID with onset prior to 18 years of age.

Monaghan et al (2020) published a "points to consider" document on the use of fetal WES in prenatal diagnosis for ACMG. This document is meant to be used as an educational resource for clinicians. There were numerous considerations stated that span from pretest to reporting, post-test, cost, reanalysis, targeted family testing, and healthcare professional education. The authors concluded that WES may be considered when a diagnosis cannot be obtained via routine prenatal methods in a fetus with anomalies.

An ACMG statement (Deignan et al., 2019, reaffirmed 2024) addressed points to consider in the reevaluation and reanalysis of genomic test results. Noting that the phenotype of impacted individuals may change or evolve over time and that information regarding the phenotypic spectrum of a condition and relevant related variants may also expand, this ACMG statement asserted that reanalysis is critical in the diagnostic odyssey. The document goes on to provide guidance to assist laboratories with developing policies and protocols on both variant and case level reevaluation and reanalysis.

American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP)

ACMG and AMP released guidance to laboratories in 2015 (Richards et al.) on how to evaluate variants found through NGS, including in WES and WGS. They also highlighted the responsibility of the ordering provider in the process, stating "due to the complexity of genetic testing, optimal results are best realized when the referring healthcare provider and the clinical laboratory work collaboratively in the testing process."

The guidelines emphasized that healthcare providers need to be prepared to provide detailed information on other lab tests performed, clinical evaluations and testing, and phenotype of the specific individual. They need to understand that some results returned (such as VUSs) may not be actionable, or the clinical implication may be unknown for pathogenic mutations. Testing of additional family members may be required to interpret the test results of the individual tested. Finally, as new data emerges, the interpretation of a variant may change over time and the healthcare provider must be prepared to monitor and manage changing interpretations. As highlighted by ACMG and AMP, "variant analysis is at present imperfect and the variant category reported does not imply 100% certainty."

American College of Obstetricians and Gynecologists (ACOG)

In the Committee Opinion 682 (2016, reaffirmed 2023), ACOG stated that "the routine use of WGS or WES for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."

Obstetric Care Consensus Number 10 (ACOG, 2020, reaffirmed 2021), addressing the management of stillbirth indicated that WES or WGS may, in the future, become part of the workup for stillbirth, but currently, this technology is not part of a standard evaluation.

ACOG's 2018 (reaffirmed 2023) Technology Assessment Number 14 addressed WES and WGS, indicating that WES is more frequently utilized in clinical genetics, as it has greater clinical relevance and applicability to patient care. The assessment noted that when standard testing from amniocentesis or chorionic villus sampling (CVS) fails to lead to a diagnosis, WES as a prenatal test may be reasonable in certain circumstances (e.g., fetuses with multiple anomalies, cases of recurrent fetal phenotypes lacking diagnosis by standard genetic tests).

American Society of Human Genetics (ASHG)

ASHG (Botkin et al., 2015) made the following recommendations pertaining to WES or WGS in children and adolescents:

- Genetic testing should be limited to single gene or targeted gene panels based on the patient's clinical presentation when appropriate.

- When targeted testing using WES or WGS is performed as an alternative to single gene or targeted panel testing, it is ethically acceptable to limit the analysis to the specific genes of clinical interest.
- WES or WGS is appropriate when prior, more limited genetic testing has failed to identify a causative variant. Under certain circumstances, WES or WGS may be appropriate as an initial genetic test.
- WES or WGS is not indicated for screening healthy children.

European Society of Human Genetics (ESHG)

Souche et al. (2022) published recommendations for use of WGS in diagnostics for rare diseases which was the result of collaboration of EuroGentest, a working group of the ESHG, and Horizon 2020 project Solve-RD which seeks to uncover genetic causes for currently unsolved rare genetic diseases using various analytical techniques. The recommendations include 44 statements which now incorporate the use of WGS, focusing on diagnostic NGS used in a clinical setting for the diagnosis of rare diseases, and address many aspects of diagnostic testing, including evaluation and rationale to setup of NGS applications including such things as quality control, variant interpretation, and reporting of NGS results. General recommendations include:

- It is recommended to introduce WGS analysis in a diagnostic setting when it is a relevant improvement on quality, efficiency and/or diagnostic yield.
- Diagnostic WGS for rare diseases and cancer (as well as other genetic testing approaches) should only be performed in accredited laboratories.
- NGS should not be transferred to clinical practice without acceptable validation of the tests.
- Confirmation, interpretation, and communication of results obtained in a research setting to the patient tested should always be done after re-testing on (preferably) an independent sample by a diagnostic laboratory.

International League Against Epilepsy (ILAE)

In 2022, Krey et al. published the ILAE recommendations for clinical genetic diagnostics in individuals with epilepsy.

- Genetic testing, as well as genetic counseling before and after testing, should be performed by appropriately qualified and trained professionals.
- In most cases, WES or WGS (including CNV analysis) is currently recommended as first-line testing.
- Periodic genetic reevaluation should be undertaken for individuals with suspected genetic epilepsy without a molecular genetic diagnosis. This includes reanalysis of previously acquired sequencing data and consideration of further testing based on new or evolving clinical information and availability of novel testing strategies.
- Genetic testing is recommended in the following conditions (provided no other clear cause has been identified):
  - Severe childhood-onset epilepsies, particularly developmental and epileptic encephalopathies.
  - Epilepsy with intellectual disability, autism, and/or other comorbidities.
  - Progressive myoclonus epilepsies and progressive phenotypes generally.
  - Non-acquired focal epilepsies in specific familial syndromes.
- Genetic testing can be considered (rather than recommended) in the following conditions:
  - Non-acquired focal, pharmacoresistant epilepsies in the setting of presurgical evaluation.
  - Epilepsy in the setting of malformations of cortical development (which may require DNA from brain tissue to be tested in parallel with DNA from another tissue source, e.g., blood or saliva).

International Society of Prenatal Diagnosis (ISPD)

In 2022, the ISPD published an updated position statement on the use of genome-wide sequencing for prenatal diagnosis, noting the rapid increase of research and clinical use of this technology for prenatal diagnosis of fetuses at risk for genetic disorders (Van den Veyver et al, 2022). Current evidence does not support routine testing of fetal tissues obtained from an invasive prenatal procedure such as amniocentesis or CVS in the absence of fetal anomalies. The position statement indicated there is data supporting the benefits of prenatal sequencing for the following:

- Current pregnancy where fetus has a major single anomaly or multiple organ system anomalies; and
  - No genetic diagnosis found after CMA and a genetic expert considers the phenotype suggestive of genetic etiology; or
  - Multiple anomaly pattern strongly suggests a single gene disorder with no prior genetic testing; CMA should be run before or in parallel with prenatal WES in this case.
- Personal history of prior undiagnosed fetus or child with a major single or multiple anomalies; and
  - Recurrence of similar anomalies in current pregnancy without genetic diagnosis after karyotype or CMA for current or prior undiagnosed pregnancy; or
  - When parents present for preconception counseling and no sample is available from the affected proband, or if a fetal sample is unable to be obtained in ongoing pregnancy, sequencing may be offered for both biological parents to look for shared carrier status of autosomal recessive mutations that could explain phenotype. Tissue from previous abnormal fetus/child for prenatal WES is preferable.

- In special circumstances, consideration of testing may be given where it would not normally be advised, such as strong family history of recurrent childhood-onset severe genetic conditions in specific circumstances, but these should be reviewed by an expert multi-disciplinary team, most appropriately in the context of a research protocol.

National Institute for Health and Care Excellence (NICE)

A 2022 (reaffirmed 2025) NICE guideline addressing epilepsies in children, young people, and adults advocated for consideration of WGS for individuals with epilepsy with no known cause who:

- Were less than two years of age at the onset of epilepsy
- Were two to three years of age at the onset of epilepsy if recommended by a specialty multidisciplinary team
- Have clinical features that suggest a specific genetic epilepsy syndrome (e.g., Dravet syndrome)
- Have clinical features such as a learning disability, autism spectrum disorder, structural abnormality (e.g., dysmorphism or congenital malformation)
- Have unexplained cognitive or memory decline

The guideline further recommended the discussion of any uncertainties around genetic testing with a geneticist or neurologist, use of the National Health Service National Genomic Test Directory (2018, updated 2024) for rare and inherited disease, and comprehensive genetic counseling with the individuals and their family/caregivers as appropriate.

National Society of Genetic Counselors (NSGC)

In a 2023 evidence-based practice guideline, the NSGC (Smith et al.) provided recommendations regarding the use of genetic testing for individuals with epilepsy, noting that a majority of unexplained epilepsy is estimated to have an underlying genetic etiology. The recommendations are as follows:

- Genetic testing with WES/WGS and/or a multi-gene panel (> 25 genes) is strongly recommended for all individuals with unexplained epilepsy, regardless of age, as first-tier testing, followed by CMA. WES/WGS is conditionally recommended over multi-gene panels.
- It is strongly recommended that genetic tests be selected, ordered, and interpreted by a qualified healthcare provider in the context of appropriate pre- and post-test genetic counseling.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Laboratories that perform genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. More information is available at: https://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm. (Accessed June 27, 2025)

A list of nucleic acid-based tests that have been cleared or approved by the FDA Center for Devices and Radiological Health is available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests. (Accessed June 27, 2025)

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Policy History/Revision Information

Date	Summary of Changes

04/01/2026	**Coverage Rationale**
	• Added language to indicate:
	  ○ Genetic counseling is recommended prior to Whole Exome Sequencing or Whole Genome Sequencing in order to inform persons being tested about the advantages and limitations of the test as applied to their unique situation
	  ○ Epigenetic signature analysis is considered unproven and not medically necessary for any indication due to insufficient evidence of efficacy
	• Replaced language indicating:
	  ○ "*Whole* genome optical mapping is considered unproven and not medically necessary" with "optical genome mapping *(OGM)* is considered unproven and not medically necessary"
	  ○ "This policy for Whole Exome and Whole Genome Sequencing (non-oncology conditions) is *limited to genetic* testing in an outpatient setting or upon discharge from an inpatient setting" with "this policy for Whole Exome and Whole Genome Sequencing (non-oncology conditions) is *applicable only* to testing in an outpatient setting or upon discharge from an inpatient setting"
	Whole Exome Sequencing (WES) or Whole Genome Sequencing (WGS) With or Without Concurrent Comparator Analysis
	• Replaced language indicating "WES/WGS is proven and medically necessary when [the listed] criteria are met" with "WES/WGS, *with or without concurrent Comparator Analysis*, is proven and medically necessary when [the listed] criteria are met"
	• Revised coverage criteria:
	  ○ Removed criterion for WGS requiring "neither chromosome microarray analysis (CMA) nor WES have been performed, or CMA/WES were nondiagnostic"
	  ○ Replaced criterion requiring:
	  ▪ "*[WES/WGS is used for] diagnosing or evaluating a genetic disorder when the results are expected to* directly *influence* medical management *and clinical outcomes*" with "*the affected individual displays signs or symptoms of an undiagnosed or unexplained disorder with a suspected* genetic *cause and the test* results are *intended* to directly *impact the individual's* medical management"
	  ▪ "The clinical presentation *is nonspecific and* does not fit a well-*defined* syndrome for which a specific or targeted *gene* test is available; if a specific genetic syndrome is suspected, a single gene or targeted *gene* panel should be performed prior to determining if WES/WGS is necessary" with "the clinical presentation does not fit a Well-*Delineated Genetic* Syndrome *or disorder* for which a specific test or a Targeted *Panel* test is available (if a specific genetic syndrome is suspected, a single gene or Targeted Panel should be performed prior to determining if WES/WGS is necessary)"
	  ▪ "The clinical *history strongly suggests a genetic cause and* [the listed criteria] *are present*" with "the clinical *presentation includes* [the listed criteria]"
	  ▪ "The clinical presentation includes multiple Congenital Anomalies (must affect different organ systems)" with "the clinical presentation includes multiple Congenital Anomalies affecting *at least two* different organ systems"
	  ▪ "The clinical presentation includes unexplained developmental regression unrelated to *autism* or epilepsy" with "The clinical presentation includes unexplained developmental regression unrelated to Autism *Spectrum Disorder* or epilepsy"
	Non-Concurrent Comparator Analysis for WES or WGS

Date	Summary of Changes

	• Revised language to indicate non-concurrent Comparator Analysis for WES or WGS is proven and medically necessary when both of the following criteria are met:
	  ○ The affected individual meets the criteria [listed in the policy] for WES or WGS
	  ○ WES or WGS has been previously performed on the affected individual
	Reanalysis of WES/WGS
	• Added language to clarify reanalysis of WES or WGS *data* is proven and medically necessary when the listed criteria are met
	• Revised coverage criteria; replaced criterion requiring:
	  ○ "At least 18 months [since the listed] criteria for initial WES or WGS *have been met*" with "at least 18 months *have passed* since the initial WES or WGS *was performed and the affected individual* meets the [listed] criteria for WES or WGS"
	  ○ "Individual experiences additional symptoms after initial WES or WGS that cannot be explained by the results of the initial *WES or WGS*" with "*the affected* individual experiences additional symptoms after initial WES or WGS that cannot be explained by the results of the initial *testing*"
	Prenatal WES
	• Revised coverage criteria; replaced criterion requiring:
	  ○ "*Sample for WES testing* is obtained from amniotic fluid and/or chorionic villi, *cultured cells from amniotic fluid/chorionic villi*, or DNA is extracted from fetal blood or tissue" with "*the specimen* is obtained from amniotic fluid and/or chorionic villi or DNA is extracted from fetal blood or tissue"
	  ○ "The fetus has multiple Congenital Anomalies (*must* affect different organ systems)" with "the fetus has multiple Congenital Anomalies affecting *at least two* different organ systems"
	  ○ "The fetus has a Congenital Anomaly affecting a single organ system and family history that suggests *likelihood* for a genetic etiology" with "the fetus has a Congenital Anomaly affecting a single organ system and family history that suggests a genetic etiology"
	Medical Records Documentation Used for Reviews
	• Added language to indicate:
	  ○ Benefit coverage for health services is determined by the federal, state, or contractual requirements, and applicable laws that may require coverage for a specific service
	  ○ Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested
	  ○ The patient's medical record must contain documentation that fully supports the medical necessity for the requested services
	  ○ This documentation includes but is not limited to relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures
	  ○ Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available upon request
	Definitions
	• Added definition of:
	  ○ Autism Spectrum Disorder
	  ○ Congenital Anomaly
	  ○ Epileptic Encephalopathy
	  ○ Targeted Panel
	  ○ Well-Delineated Genetic Syndrome
	• Removed definition of:
	  ○ Next Generation Sequencing (NGS)
	  ○ Variant of Unknown Significance (VUS)
	• Updated definition of:
	  ○ Comparator Analysis
	  ○ Global Developmental Delay
	  ○ Intellectual Disability
	  ○ Preimplantation Genetic Testing (PGT)
	Applicable Codes
	• Added CPT codes 0318U, 0582U, 0583U, and 81354
	Supporting Information

Date	Summary of Changes
	• Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS150NM.D

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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