Prenatal Exome and Genome Sequencing

Effective Date: May 2026

Executive Summary:

This medical coverage policy addresses the use of prenatal exome sequencing (pES) and prenatal genome sequencing (pGS). Rare diseases affect approximately 1 in 10 Americans, with the majority having an identified genetic etiology; some genetic disorders are associated with anomalies detectable prenatally. pES/pGS are powerful diagnostic tools that provide an incremental diagnostic yield of approximately 30% beyond routine testing (e.g., karyotype, chromosomal microarray) and sequencing results frequently influence clinical decision-making. These tests are considered medically necessary for pregnancies meeting specific criteria, including a major single anomaly, multiple organ system anomalies, or fetal hydrops of unknown etiology. The policy emphasizes the importance of pre- and post-test counseling to ensure families make informed decisions, understand the benefits and limitations of testing, and receive appropriate psychosocial support throughout the diagnostic process.

Criteria:

Prenatal exome sequencing (pES) or prenatal genome sequencing (pGS) is considered medically necessary when ALL THREE of the following criteria are met:

1. The sample for testing is obtained from amniotic fluid or chorionic villi, cultured cells from amniotic fluid/chorionic villi, or from DNA extracted from fetal blood or tissue,
2. The current pregnancy has one or more of the following:
    - A major single anomaly* or multiple organ system anomalies
    - Non-immune hydrops fetalis of unknown etiology
    - A single organ system anomaly with a family history suggestive of a genetic etiology
3. One of the following diagnostic pathways applies:
    - Aneuploidy assessment using standard diagnostic genetic testing (e.g., karyotype, chromosomal microarray) is uninformative, OR
    - pES/pGS performed as an initial diagnostic test in conjunction with a board-certified maternal–fetal medicine specialist, clinical geneticist, or genetic counselor, AND ONE of the following criteria is met:
        i. Delays due to sequential testing could affect pregnancy or delivery management (e.g., gestational age or clinical urgency)
        ii. The fetal phenotype strongly suggests a single-gene disorder and the likelihood of common aneuploidy is low based on prior screening, ultrasound findings, or expert clinical assessment.

*Congenital anomalies are structural or functional abnormalities present at birth that encompass a wide spectrum of conditions varying in severity. Major anomalies can significantly impact an infant's life expectancy, health status (e.g., require medical or surgical treatment), and long-term physical or social functioning (not

applicable in the prenatal setting).[1] Examples of major anomalies that can be detected prenatally include, but are not limited to:[2-4]

- Genitourinary: renal agenesis, multicystic kidney dysplasia, differences of sexual development
- Cardiovascular: transposition of the great arteries, tetralogy of Fallot, coarctation of the aorta
- Musculoskeletal: shortened long bones, arthrogryposis, prenatal fractures
- Central nervous system: anencephaly, holoprosencephaly, lissencephaly, agenesis of the corpus callosum
- Gastrointestinal/body wall: omphalocele, congenital diaphragmatic hernia, bladder exstrophy

Exclusions and Other Considerations:

Exclusions:

- pES/pGS are considered not medically necessary in pregnancies who do not meet the above criteria.
- pES/pGS is not appropriate for fetuses at risk for a known familial variant unless one of the following criteria are met:
  - targeted genetic testing has been performed and is negative, OR
  - the ultrasound findings are not consistent with the familial condition.
- pES/pGS is considered experimental/investigational for fetuses with no anomalies.

Other Considerations:

- Maternal cell contamination analysis can be performed with pES/pGS to ensure the tested DNA accurately reflects the fetus.
- Professional society statements regarding pES/pGS are mixed. The statements based on the most extensive and recent literature reviews (within the last 5 years) support the use of pES/pGS.[5]
- While ES and GS are similar diagnostic tools in prenatal evaluation, there are clear technical advantages of GS that support increased diagnostic yield and efficiencies. For example, GS typically requires a smaller quantity of DNA and provides better copy number variant (CNV) detection. As such, if given a choice, pGS is the preferred diagnostic test for fetuses who meet the above criteria.
- Trio samples are preferred for ES and GS as their inclusion can increase the diagnostic yield by approximately 10-15% and reduces the rate of variants of uncertain significance by ~9% in postnatal studies.[6-8]
- Turnaround time for testing varies depending on multiple factors, including the specific laboratory performing the analysis, the test type (ES vs. GS), and whether cell culture is necessary prior to testing.
- Postnatal ES/GS is not addressed in this policy. Criteria can be found in the Exome and Genome Sequencing for Rare Disease or Rapid Genome Sequencing policies.

- This policy does not address ES/GS for miscarriages, intrauterine fetal demise (IUFD), or stillbirth.
- To ensure results are not delayed by the clinical urgency of this testing in the prenatal setting, prior authorization should not be mandated as a prerequisite for coverage.

Background:

Approximately 1 in 10 Americans, an estimated 30 million individuals, are affected by rare diseases. It is estimated that 72% of rare diseases have an identified genetic etiology.[9] Some of these conditions are associated with anomalies that are detectable prenatally. Congenital anomalies occur in about 2-4% of pregnancies, and many are detectable by ultrasound. Prenatal diagnostic testing for underlying genetic causes can be performed using fetal cells from amniotic fluid or percutaneous umbilical blood sampling (PUBS) (cordocentesis), or from placental cells via chorionic villus sampling (CVS). Conventional chromosome analysis (karyotype) or chromosomal microarray analysis (CMA) is routinely performed for aneuploidy assessment. Additionally, copy number variants (CNVs; deletions and duplications) can be identified by CMA with higher resolution than karyotype.[10] The diagnostic yield of CMA across high-risk prenatal indications is about 7-15%, though this varies substantially by indication.[11-13] Evaluation of single-gene disorders as an underlying cause of prenatally identified anomalies can be done by single-gene or multigene panels, typically via Sanger sequencing or next-generation sequencing (NGS).[14] The diagnostic yield varies widely and is highly dependent on the specific clinical indication and population studied. Advances in sequencing technologies have led to the emergence of exome sequencing (ES) and genome sequencing (GS) as more comprehensive prenatal diagnostic approaches, enabling detection of an increasing number of genetic conditions.[10,14]

Technical Information:

Genomic sequencing technologies currently utilized in clinical practice include ES and GS. ES and GS are similar diagnostic tools in the evaluation for rare disease, but there are clear technical advantages of GS that support increased diagnostic yield and efficiencies as outlined below. In the postnatal space, GS is becoming the preferred diagnostic test, and the same advantages that have led to widespread use are present in prenatal diagnosis.[10,15]

ES is a capture-based method that targets the DNA sequence of coding regions (exons) and flanking intronic regions of 1-2% of the genome. ES is associated with technical and analytical variability, including uneven sequencing coverage and gaps in exon capture before sequencing. In contrast, GS involves shearing and sequencing all intergenic and intragenic regions, eliminating the need for a capture step, which increases efficiency and minimizes PCR-based artifacts. Both ES and GS can identify the following categories of pathogenic variants: missense, nonsense, splice-site, and small deletions or insertions. GS is advantageous as a diagnostic tool

due to uniformity of coverage, including GC-rich regions, as well as the ability to detect variants that may be missed by ES, such as some copy-number variants (CNVs), mid-size insertions and deletions (~10-500 bp), nucleotide repeat expansion variants, deeper intronic variants, structural variants (e.g., translocations, inversions), variants in the mitochondrial genome, and uniparental disomy.[15,16]

The use of ES and GS in prenatal diagnosis has historically lagged behind postnatal adoption due to turnaround times that preclude returning results within the pregnancy timeframe, and incomplete or unrecognized fetal phenotypes that complicate prenatal interpretation of genetic variants.[17] However, technological improvements to reduce result turnaround times and increasing clinical experience with prenatal and postnatal cases have resulted in broader adoption of pES and pGS into clinical practice.[10]

Guidelines:

American College of Medical Genetics and Genomics (ACMG)

- ACMG has several relevant policy statements that offer guidance on informed consent for ES/GS,[18] technical standards to ensure quality results and the interpretation and reporting of variants,[19] reporting of secondary findings in clinical ES/GS,[20] and re-analysis.[21]
- ACMG issued an educational resource stating, "Exome sequencing may be considered for a fetus with ultrasound anomalies when standard CMA and karyotype analysis have failed to yield a definitive diagnosis." The resource acknowledges that "GS may be more informative due to its scope" but is "not routinely utilized in clinical testing at this time."[22]

American College of Obstetricians and Gynecologists (ACOG)

- ACOG committee opinion in collaboration with the Society for Maternal Fetal Medicine (SMFM) from 2016 and reaffirmed in 2023 states, "routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published."[23]
- ACOG technology assessment from 2018 and reaffirmed in 2023 states that pES should be considered after non-diagnostic standard genetic testing in fetuses with multiple anomalies or recurrent fetal phenotypes. ACOG stated that GS "is not routinely being performed in clinical practice."[24]

International Society for Prenatal Diagnosis (ISPD) with Society for Maternal Fetal Medicine (SMFM)

- ISPD with endorsement by SMFM issued a joint statement in 2022 stating that data supports pES and pGS in a pregnancy with a fetus having a major single anomaly or multiple organ system anomalies[5]

- for which no genetic diagnosis was found after CMA and a clinical genetic expert review considers the phenotype suggestive of a possible genetic etiology, or
- for which the multiple anomaly "pattern" strongly suggests a single gene disorder with no prior genetic testing. CMA should be run before or in parallel with pES in this scenario since pES is not currently validated to detect all CNVs.

Society for Maternal Fetal Medicine (SMFM)

- SMFM guidance from 2026 recommends that, "exome or genome sequencing be offered in pregnancies with NIHF [non-immune hydrops fetalis] or NIHF spectrum following CMA or karyotype that does not yield a diagnosis and in the absence of another suspected etiology."
- SMFM further states that if the risk of aneuploidy is low or a single-gene disorder is strongly suspected, offering exome or genome sequencing concurrently with CMA is reasonable, particularly when timely diagnosis may influence pregnancy management.[25]

Evidence:

The diagnostic yield of pES and pGS varies based on fetal findings but overall is about 30% beyond routine testing (karyotype and/or CMA).[10] Studies demonstrate the diagnostic yield of pES/pGS is typically at least 2 to 3 times higher than CMA.[26,27]

Congenital Anomalies

Multiple meta-analyses and studies have been published on thousands of pregnancies evaluated using pES and/or pGS. The incremental yield of pES/pGS over CMA/karyotype is about 30%.[10,17,28]

The diagnostic yield for pES/pGS varies by subgroup with the highest yield reported in fetuses with

- Skeletal anomalies: ~53% to 69%[17,29-31]
- Neuromuscular anomalies: ~37%[17]
- Multisystem anomalies: ~27% to 29%[17,26]
- Central nervous system anomalies: 17% to 36%[17,26,27,32-34] including agenesis of the corpus callosum: 23% to 43%[35,36] and bilateral severe ventriculomegaly: 54%[37]
- Congenital heart disease: 17% to 21%[38,39]

Dynamic Abnormalities

Dynamic abnormalities are anomalies that may regress or progress during pregnancy and do not fit the standard definitions of structural anomalies or soft markers. These include quantitative changes of amniotic fluid (e.g., anhydramnios, oligohydramnios and polyhydramnios), fetal growth restriction (FGR), effusions (e.g., hydrops, pleural or pericardial effusions, ascites) and cystic hygroma.[26]

Non-immune Hydrops Fetalis (NIHF)
Hydrops is characterized by abnormal fluid collection in two or more fetal compartments including ascites, pleural effusions, pericardial effusion, and generalized skin edema. NIHF is hydrops not caused by red cell alloimmunization. NIHF is a heterogeneous condition with an extensive differential diagnosis including many underlying genetic conditions. An accurate diagnosis is critical for determining prognosis and recurrence risk. It is associated with a high risk of stillbirth, preterm birth, and neonatal complications or death.[25] Studies have demonstrated a diagnostic yield of pES of ~22% to 37%.[17,26,40,41]

Fetal growth restriction (FGR)
Studies have also reported use of pES after a nondiagnostic CMA/karyotype for FGR during pregnancy:

- in absence of fetal structural anomalies: 4%-12%[42,43]
- with additional structural anomalies: 30%[43]

Abnormal amniotic fluid volume
One study reported diagnostic yield of pES in polyhydramnios: 3%[26]

Isolated Increased Nuchal Translucency
Studies have also reported use of pES after a nondiagnostic CMA/karyotype for apparently isolated increased nuchal translucency with diagnostic yield of ~5% to 13%.[26,44,45]

Non-anomalous
Prenatal exome studies of fetuses with no ultrasound abnormalities, performed for parental request, have reported a diagnostic yield of <1%.[46]

Clinical and Personal Utility
pES/pGS frequently leads to changes in clinical management. In a study of pregnancies with congenital anomalies, physicians reported that pES results influenced clinical decision-making in approximately 70% of pregnancies; another study reported a clinical impact in over 60% of pregnancies.[47,48] Examples of how pES/pGS impacts care include:[10,17,49-51]

- Informing reproductive decision-making, fetal prognosis, and expected outcomes
- Guiding perinatal management strategies that can mitigate irreversible harm and life-threatening complications, fetal therapy, and immediate targeted dietary or medication interventions
- Optimizing delivery planning (mode, timing, location) and coordinated multidisciplinary care for immediate condition-specific intervention
- Avoiding sequential testing approaches and unnecessary procedures which may include transition to palliative care
- Reducing healthcare costs

- Providing accurate recurrence risk counseling and informing future reproductive planning and family counseling

Prenatal Counseling, Variant Interpretation, and Postnatal Follow-up

- While requirements for ordering providers may limit access to care, pre- and post-test counseling is essential to ensure families make informed decisions, appreciate the benefits and limitations of testing, potential outcomes, receive clear and accurate interpretation of results and their implications, and receive psychosocial support.[10,52]
- Variant interpretation may be more challenging in the prenatal setting due to limited clinical assessment during pregnancy, features that may not have developed yet, and less knowledge about features of genetic disorders during pregnancy. Reporting uncertain results can be difficult for families and further supports the importance of counseling.[10] Laboratories may differ on reporting policies for variants of uncertain significance (VUS).
- ES and GS can identify incidental or secondary findings such as hereditary cancer predisposition or cardiovascular risks. Pre-test counseling should include considerations of opting out or delaying the return of secondary findings.
- Postnatal re-analysis after additional evaluations resolves approximately 30-44% of variants of uncertain significance (VUS). Coordination with neonatal providers and genetic re-analysis after birth is recommended if there are new postnatal findings or changes in the family history.[10,53]

CPT codes:

CPT Code	Description
81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Sequence analysis, each comparator exome (e.g., parent(s), sibling(s))
81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Sequence analysis, each comparator genome (e.g., parent(s), sibling(s))
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
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)
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

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