



# GENETIC TESTING: PRENATAL DIAGNOSIS (via Amniocentesis CVS or PUBS) and PREGNANCY LOSS (PREAUTHORIZATION REQUIRED)

V.30

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### DESCRIPTION

Prenatal diagnostic testing may be used to identify genetic conditions in fetuses at an increased risk based on prenatal screening or for women who choose to undergo diagnostic testing due to other risk factors, such as abnormal ultrasound findings, previous pregnancy with aneuploidy, etc. Prenatal diagnostic testing for genetic disorders is performed on fetal cells derived from amniotic fluid, and/or [percutaneous umbilical blood sampling \(PUBS\)](#) (cordocentesis) or from placental cells via [chorionic villus sampling \(CVS\)](#). Genetic testing techniques include conventional chromosome analysis, chromosome fluorescence in situ hybridization (FISH), chromosomal microarray analysis (CMA), targeted or Sanger sequencing, and next-generation sequencing (NGS). Exome and genome sequencing are also emerging as new prenatal diagnostic tools.

Genetic testing may also be used in an attempt to determine the cause of isolated or [recurrent pregnancy loss](#), including miscarriages, intrauterine fetal demise (IUFD), and stillbirth. The evaluation of both recurrent and isolated miscarriages and IUFD or stillbirth may involve genetic testing of the products of conception (POC) and/or testing of fetal/placental cells from amniotic fluid, CVS, or PUBS if available. Such testing of POC has typically been carried out through cell culture and karyotyping of cells in metaphase. However, the analysis of fetal or placental tissue has been inhibited by the following limitations: the need for fresh tissue, the potential for cell culture failure, and the potential for maternal cell contamination. Potential benefits of identifying a genetic



for future pregnancies.

The decision to elect a prenatal diagnostic test and/or genetic testing following pregnancy loss should be made jointly by the mother and/or parents and the treating clinician. Genetic counseling, including facilitation of decision making, is strongly recommended.

In most cases, prenatal genetic testing for single gene disorders using molecular genetic testing requires knowledge of the familial genetic variant which has been identified in a family member (e.g., biological mother, biological father, and/or sibling).

Dates

Original Effective  
**03-11-2016**  
Last Review  
**08-07-2024**  
Next Review  
**08-11-2025**

REFERENCE TABLE

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the [Concert Platform](#) for a comprehensive list of registered tests.

<a href="#">Coverage Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	
<a href="#">Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis</a>	Reveal SNP Microarray - Prenatal (Integrated Genetics)	81228, 81229, 81265	O26.2, O28, Q00-Q99, Z14.8	
	Prenatal Whole Genome Chromosomal Microarray (GeneDx)			
	IriSight CNV Analysis (Variantyx)	0469U		
<a href="#">Chromosomal Microarray Analysis (CMA) for Pregnancy Loss</a>	SNP Microarray-Products of Conception (POC)/Tissue (Reveal) (Labcorp)	81228, 81229, 81265	O03, Z37	



<a href="#">Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies</a>	Prenatal Noonan Spectrum Disorders Panel (GeneDx)	81404, 81405, 81406, 81407,	O28.3, O35.8XX0	
	Prenatal Noonan Syndrome (Integrated Genetics)	81479, 81442, 81265		
<a href="#">Prenatal Diagnosis for Skeletal Dysplasias</a>	Prenatal Skeletal Dysplasia Panel (GeneDx)	81404, 81405, 81408, 81479,	O35.8XX0, O28.3	
	Skeletal Dysplasia Core NGS Panel (Connective Tissue Gene Tests)	81265		
<a href="#">Prenatal Diagnosis via Exome Sequencing</a>	XomeDx Prenatal - Comprehensive (GeneDx)	81415, 81416, 81265	O35.8XX0, O28.3	
	Prenatal Exome Sequencing (Greenwood Genetic Center - Molecular Diagnostic Laboratory)			
<a href="#">Prenatal Diagnosis via Genome Sequencing</a>	Prenatal Whole Genome Sequencing	81425, 81426, 81427, 81265	O35.8XX0, O28.3	
	IriSight Prenatal Analysis (Variantyx)	0335U, 0336U		
	Rapid Genome Sequencing Test (Genomic Med Lab)	0532U		

## RELATED POLICIES

This policy document provides coverage criteria for prenatal or pregnancy loss diagnostic testing, and does not address the use of CMA, preimplantation genetic testing or the evaluation of suspected chromosome abnormalities in the postnatal period. Please refer to:

- **V.17 Genetic Testing: Prenatal Cell-free DNA Testing** for coverage criteria related to prenatal cell-free DNA screening tests.
- **V.31 Genetic Testing: Prenatal and Preconception Carrier Screening** for coverage criteria related to carrier screening for genetic disorders.
- **V.75 Genetic Testing: Preimplantation Genetic Testing** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.



- **V.74 Genetic Testing: General Approach to Genetic Testing** for coverage criteria related to prenatal diagnostic or pregnancy loss genetic testing that is not specifically discussed in this or other non-general policies, including known familial variant testing.

## POLICY

### CHROMOSOMAL MICROARRAY ANALYSIS (CMA) FOR PRENATAL DIAGNOSIS

I. Chromosome microarray analysis (81228, 81229, 81265, 0469U) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when:

A. The member has received counseling regarding the benefits and limitations of prenatal screening and diagnostic testing (including chromosome microarray via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities.

II. Chromosome microarray analysis (81228, 81229, 81265, 0469U) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications.

### CHROMOSOMAL MICROARRAY ANALYSIS (CMA) FOR PREGNANCY LOSS

I. Chromosomal microarray analysis (81228, 81229, 81265) on products of conception (POC) may be considered **medically necessary** as an alternative to conventional karyotype analysis when:

A. The member meets one of the following:

1. The member has a history of recurrent pregnancy loss **OR**
2. The member has a pregnancy loss at or greater than 20 weeks of gestation (i.e., IUFD or stillbirth) **AND**

B. The member has received counseling regarding the benefits and limitations of chromosome microarray analysis on products of conception.

II. Chromosome microarray analysis (81228, 81229, 81265) on products of conception (POC) is considered **investigational** when the above criteria is not met and for all other indications.



I. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81407, 81479, 81442, 81265) may be considered **medically necessary** when:

A. The member's current pregnancy has a normal karyotype and/or microarray **AND**

B. The member meets **one** of the following:

1. The member's current pregnancy has an ultrasound finding of increased nuchal translucency or cystic hygroma of at least 5.0mm in the first trimester, **OR**

2. The member's current pregnancy has both of the following:

a. An increased nuchal translucency of at least 3.0 mm, **AND**

b. **One** of the following ultrasound findings:

(1) Distended jugular lymph sacs  
(JLS), **OR**

(2) Hydrops fetalis, **OR**

(3) Polyhydramnios, **OR**

(4) Pleural effusion, **OR**

(5) Cardiac defects (e.g., pulmonary valve stenosis, atrioventricular septal defect, coarctation of the aorta, hypertrophic cardiomyopathy, atrial septal defect, etc.)

II. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81407, 81479, 81442, 81265) is considered **investigational** if the above criteria is not met and for all other indications.

## **PRENATAL DIAGNOSIS FOR SKELETAL DYSPLASIAS**

I. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408,



ultrasound findings:

1. Long bones less than 5th percentile, **OR**
2. Poor mineralization of the calvarium, **OR**
3. Fractures of long bones (particularly femora), **OR**
4. Bent/bowed bones, **OR**
5. Poor mineralization of the vertebrae, **OR**
6. Absent/hypoplastic scapula, **OR**
7. Equinovarus, **AND**

B. The panel being ordered includes, at a minimum, the following genes: *COL1A1*, *COL1A2*, *COL2A1*, *FGFR3*.

II. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265) is considered **investigational** for all other indications.

#### **PRENATAL DIAGNOSIS VIA EXOME SEQUENCING**

I. Prenatal diagnosis via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265) may be considered **medically necessary** when:

A. The member's current pregnancy has had a karyotype and/or microarray performed and the results were negative/normal, **AND**

B. Alternate etiologies have been considered and ruled out when possible (examples: environmental exposure, injury, infection, maternal condition), **AND**

C. The member's current pregnancy has had either of the following:

1. Non-immune hydrops fetalis, **OR**
2. Two of more major malformations on ultrasound, which are affecting different organ systems.

II. Prenatal diagnosis via amniocentesis, CVS, PUBS using exome sequencing (81415, 81416, 81265) is considered **investigational** for all other conditions



genomic sequencing (01420, 01420, 01421, 01420, 00000, 00000, 0532U) is considered **investigational**.

## DEFINITIONS

**Major malformations** are structural defects that have a significant effect on function or appearance. They may be lethal or associated with possible survival with severe or moderate immediate or long-term morbidity. Examples by organ system include:

- Genitourinary: renal agenesis (unilateral or bilateral), hypoplastic/cystic kidney
- Cardiovascular: complex heart malformations (such as pulmonary valve stenosis, tetralogy of fallot, transposition of the great arteries, coarctation of the aorta, hypoplastic left heart syndrome)
- Musculoskeletal: osteochondrodysplasia/osteogenesis imperfecta, clubfoot, craniosynostosis, fetal growth restriction/intrauterine growth restriction (IUGR)
- Central nervous system: anencephaly, hydrocephalus, myelomeningocele
- Body wall: omphalocele/gastroschisis
- Respiratory: cystic adenomatoid lung malformation

**Amniocentesis** is a procedure in which a sample of amniotic fluid is removed from the uterus for prenatal diagnostic testing.

**Chorionic Villi Sampling (CVS)** is a procedure where a sample of chorionic villi is removed from the placenta for prenatal diagnostic testing.

**Percutaneous Umbilical Cord Blood Sampling (PUBS)** is a procedure where a sample of fetal blood is extracted from the vein in the umbilical cord.

**Recurrent pregnancy loss (RPL)** is defined as having two or more failed clinical pregnancies, including a current loss if applicable.

## BACKGROUND

### Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis



following.

-Chromosomal aberrations that are smaller than the resolution of conventional karyotype also can result in phenotypic anomalies; these copy number variants can be detected in the fetus using chromosomal microarray analysis. When structural abnormalities are detected by prenatal ultrasound examination, chromosomal microarray will identify clinically significant chromosomal abnormalities in approximately 6% of the fetuses that have a normal karyotype. For this reason, chromosomal microarray analysis should be recommended as the primary test (replacing conventional karyotype) for patients undergoing prenatal diagnosis for the indication of a fetal structural abnormality detected by ultrasound examination. (p. e109)

-Chromosomal microarray analysis has been found to detect a pathogenic (or likely pathogenic) copy number variant in approximately 1.7% of patients with a normal ultrasound examination and a normal karyotype, and it is recommended that chromosomal microarray analysis be made available to any patient choosing to undergo invasive diagnostic testing. (p. e.110)

ACOG practice bulletin #226 (2020) states the following regarding counseling patients: "Each patient should be counseled in each pregnancy about options for testing for fetal chromosomal abnormalities. It is important that obstetric care professionals be prepared to discuss not only the risk of fetal chromosomal abnormalities but also the relative benefits and limitations of the available screening and diagnostic tests." (p. 859)

### **Conventional Karyotype Analysis for Prenatal Diagnosis**

*American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal Fetal Medicine (SMFM)*

The ACOG and SMFM practice bulletin (#226, 2020) states the following:

"Prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality." (p. 862)

"Each patient should be counseled in each pregnancy about options for testing for fetal chromosomal abnormalities. It is important that obstetric care professionals be prepared to discuss not only the risk of fetal





*American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal Fetal Medicine (SMFM)*

The ACOG and SMFM practice bulletin (#682) supports the following evaluation for pregnancy loss in their 2016 statement (reaffirmed 2020 and 2023):

“Chromosomal microarray analysis of fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended in the evaluation of intrauterine fetal death or stillbirth when further cytogenetic analysis is desired because of the test’s increased likelihood of obtaining results and improved detection of causative abnormalities.” (p. e263)

*American Society for Reproductive Medicine (ASRM)*

The American Society for Reproductive Medicine (2012) issued an opinion on the evaluation and treatment of recurrent pregnancy loss. The statement drew multiple conclusions, one of which states: “Evaluation of recurrent pregnancy loss can proceed after 2 consecutive clinical pregnancy losses.” (p. 1108)

*Papas and Kutteh (2021)*

A review published in the Application of Clinical Genetics in 2021 by Papas and Kutteh recommends that genetic testing on products of conception should be performed after the second and subsequent pregnancy loss. Chromosome microarray is the preferred testing method. (p. 321)

### **Conventional Karyotype Analysis for Pregnancy Loss**

*American Society for Reproductive Medicine (ASRM)*

According to the ASRM’s 2012 statement, recurrent pregnancy loss (RPL) is defined as a distinct disorder defined by two or more failed clinical pregnancies. Evaluation of RPL can proceed after two consecutive clinical pregnancy losses, which may include karyotypic analysis of products of conception (p. 1103 and 1108) For the purposes of this committee, the ASRM defines clinical pregnancy as “...documented by ultrasonography or histopathological examination.” (p. 1103)

### **Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies**

*Stuurman KE, Joosten M, van der Burgt I, et al, 2019*



when the NT is greater than or equal to 5.0 mm. We also recommend testing when the NT is greater than or equal to 3.5 mm and at least one of the following anomalies is present: distended jugular lymph sacs (JLS), hydrops fetalis, polyhydramnios, pleural effusion and cardiac defects.” (p. 660)

“In general, an NGS panel of known rasopathy genes should be used when a rasopathy is suspected. Although we did not find pathogenic variants in every gene in the panel, in all genes, a prenatal phenotype has been documented in literature. Therefore, a smaller panel is not advisable. However, in countries where an extensive panel is not available, testing for only *PTPN11* gene would catch at least 50% of the fetuses with a rasopathy.” (p. 661)

#### *American College of Obstetricians and Gynecologists*

The ACOG and SMFM practice bulletin (#226, 2020) defines an enlarged nuchal translucency (NT) as 3.0 mm or more or above the 99<sup>th</sup> percentile for the crown–rump length). (p. e53)

#### *GeneReviews: Noonan Syndrome*

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The clinical summary for Noonan Syndrome gives the following prenatal features (Roberts, 2022):

- Polyhydramnios
- Lymphatic dysplasia including increased distended jugular lymphatic sacs, nuchal translucency, cystic hygroma, pleural effusion, and ascites
- Relative macrocephaly
- Cardiac and renal anomalies

The author points out that 3%-15% of chromosomally normal fetuses with increased nuchal translucency have *PTPN11*-associated Noonan syndrome.

#### **Prenatal Diagnosis for Skeletal Dysplasias**

##### *Krakow et al 2009*

A guideline for prenatal diagnosis of fetal skeletal dysplasias (Krakow, Lachman, Rimoin, 2009) recommends the follow criteria:

- Fetuses with long bone measurements at or less than the 5<sup>th</sup> centile or greater than 3 SD below the mean should be evaluated in a center



or ectopic mineralization). Determining the elements of the skeleton that are abnormal, coupled with the findings of mineralization and shape of the bones can aid in diagnosis. (p. 3)

The guideline also lists several other common abnormal ultrasound findings in Table 2, including fractures of long bones (primarily femora), poor mineralization of the vertebrae, bent/bowed legs, and absent/hypoplastic scapula, as additional ultrasound findings that would prompt evaluation. (p. 10)

*Scocchia, et al.*

A 2021 study of the clinical utility of multigene panel testing for an unselected population of individuals with suspected skeletal dysplasia demonstrated a high diagnostic yield in prenatal cases. (p. 1)

A molecular diagnosis was established in 42% of patients (228/543). Diagnostic variants were identified in 71 genes, with variation in nearly half of these genes contributing to a molecular diagnosis for a single patient in this cohort. Overall, the most common genes in which molecular diagnoses were identified included: *COL2A1* associated with type II collagenopathies; *FGFR3* associated with achondroplasia, thanatophoric dysplasia, hypochondroplasia, and other conditions such as FGFR-related craniosynostoses; and *COL1A1* or *COL1A2*, associated with osteogenesis imperfecta. Together, these four genes accounted for over one third of all molecular diagnoses across the cohort. (p. 2-3)

### **Prenatal Diagnosis via Exome Sequencing**

*American College of Medical Genetics and Genomics (ACMG)*

ACMG issued a statement on the use of fetal exome sequencing in prenatal diagnosis (2020) that included the following points to consider:

- “Exome sequencing may be considered for a fetus with ultrasound anomalies when standard CMA and karyotype analysis have failed to yield a definitive diagnosis. If a specific diagnosis is suspected, molecular testing for the suggested disorder (with single-gene test or gene panel) should be the initial test. At the present time, there are no data supporting the clinical use for ES for other reproductive indications, such as the identification of sonographic markers suggestive of aneuploidy or a history of recurrent unexplained pregnancy loss.” (p. 676)
- “Pretest counseling is ideally provided by a genetics professional during which the types of variants that may be returned in a



maintain all aspects of reproductive choice. A rapid turnaround time has been demonstrated in the postnatal setting for critical genetic diagnoses in a pediatric and neonatal setting. Laboratories offering prenatal ES should have clearly defined turnaround times for this time-sensitive test.” (p. 677)

-“Post-test counseling is recommended, regardless of the test result. It should be provided by individuals with relevant expertise, preferably a genetics professional.” (p. 678)

-The statement also indicates that the detection rate of fetal anomalies is proportional to the severity of phenotype, with a range of 6% for fetuses with a single anomaly to 35% of fetuses with more than two anomalies. (p. 676)

*Al-Kouatly, et al 2022*

“We performed a systematic literature review and meta-analysis focusing specifically on ES in cases of NIHF to determine the contribution of monogenic etiologies.” (p.504)

“In our meta-analysis, greater than one-third (37%) of cases of NIHF with negative clinical workup for anemia, infections, and chromosomal disorders have a monogenic disorder detectable by ES providing clarification of etiological category (e.g., syndromic, neuromuscular, metabolic, etc.) and inheritance pattern (e.g., autosomal dominant de novo, autosomal dominant inherited, autosomal recessive, or X-linked).” (p. 507)

“ES should be considered in the diagnostic workup of NIHF with and without associated ultrasound findings regardless of history of recurrence or consanguinity.” (p. 503-504)

### **Prenatal Diagnosis Via Genome Sequencing**

*American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal Fetal Medicine (SMFM)*

ACOG and SMFM (2016, reaffirmed in 2020 and 2023) issued a committee opinion No. 682, which included the following conclusions and recommendations for the use of chromosomal microarray testing and next-generation sequencing in prenatal diagnosis. *Note that while whole exome sequencing is addressed in this opinion, whole genome sequencing is not yet recommended:*

“Whole-exome sequencing also is a broad molecular diagnostic approach to identify the etiology for fetal abnormalities, and whole-exome



However, the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published. ” (p. 4)

*Zhou J, et al. 2021*

An article by Zhou, et al prospectively evaluated the clinical utility of whole genome sequencing (WGS) compared with standard chromosome microarray (CMA) in fetuses with structural anomalies. WGS was found to have a diagnostic rate of 19.8%, and was able to provide additional clinical information, such as a balanced translocation. “ The article concludes by saying that “with a rapid TAT, good diagnostic yield, and less DNA required, WGS could be an alternative test in lieu of two separate analyses as it has an equivalent diagnostic yield to that of CMA plus WES and provides comprehensive detection of various genomic variants in fetuses with structural or growth anomalies. However, more prospective studies with larger cohorts and further evaluation are warranted to demonstrate the value of WGS in prenatal diagnosis.” (p. 12)

## RECOMMENDED MEDICAL RECORDS

- History and Physical Report
- Office Notes
- Genetic Counseling Documentation

## Quick Code Search

Use this feature to find out if a procedure and diagnosis code pair will be approved, denied or held for review. Simply put in the procedure code, then the diagnosis code, then click "Add Code Pair". If the codes are listed in this policy, we will help you by showing a dropdown to help you.

### Procedure

Enter at least the first 3 characters of the code

### Diagnosis

Enter at least the first 3 characters of the code



**CODES**

+ **CPT-PLA**

+ **CPT4**

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## 2024

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# REVISIONS



**01-01-2025**

Codes updated. Removed Prenatal Diagnosis for single gene disorder section. Updated prenatal diagnosis via exome sequencing criteria. Background and references updated.

**06-28-2024**

Added new 07/01/2024 PLA code: 0469U

**12-13-2023**

Updated policy criteria for 01/01/2023

**09-27-2023**

Changed "may be considered medically necessary" to "may be considered scientifically validated"

Added: "investigational when the above criteria is not met and for all other indications"

**06-01-2023**

Criteria updated: Noonan Spectrum Disorders/RASopathies, formatting and reference updates.

**01-01-2023**

Updated reference table and criteria for chromosome microarray analysis for prenatal diagnosis. Background and references updated.

**09-15-2022**

Added new codes effective 10/01/2022: 0335U and 0336U as investigational

**07-01-2022**

Updated formatting and reference table

**01-01-2022**

Updated references and background and reviewed/updated codes

**07-01-2021**

Added criteria for Skeletal Dysplasias, Noonan Spectrum Disorders and Prenatal diagnosis via exome sequencing.

**05-17-2021**

Added new 07/01/2021 code: 0252U



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