

# GENETIC TESTING: PRENATAL DIAGNOSIS (VIA AMNIOCENTESIS, CVS, OR PUBS) AND PREGNANCY LOSS

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## OVERVIEW

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).

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 abnormality in a miscarriage or IUFD include reducing emotional distress for families, eliminating the need for additional testing to assess for causes of pregnancy loss, and assisting in reproductive decision making for future pregnancies.

## POLICY REFERENCE TABLE

<a href="#">Coverage Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	<a href="#">Ref</a>
<a href="#">Chromosomal FISH (Aneuploidy) Analysis</a>	Aneuploidy Panel by FISH (ARUP Laboratories)	81265, 88230, 88235, 88271, 88275, 88291	O26.2, O28, Q00-Q99, Z14.8	3
<a href="#">Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis</a>	Reveal® SNP Microarray - Prenatal (Integrated Genetics)	81228, 81229, 81265, 88235	O26.2, O28, Q00-Q99, Z14.8	3
	Prenatal Whole Genome Chromosomal Microarray (GeneDx)			
<a href="#">Conventional Karyotype Analysis for Prenatal Diagnosis</a>	Chromosome Analysis, Amniotic Fluid (GeneDx)	88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291	O26.2, O28, Q00-Q99, Z14.8	9
	Chromosome Analysis, Chorionic Villus Sample (Quest Diagnostics)			
	Chromosome Analysis, Amniotic Fluid (Quest Diagnostics)			
<a href="#">Chromosomal Microarray Analysis (CMA) for Pregnancy Loss</a>	SNP Microarray-Products of Conception (POC)/Tissue (Reveal) (LabCorp)	81228, 81229, 81265, 88235	O03, Z37	1, 2, 11
	Chromosomal Micorarray, POC, ClariSure Oligo-SNP (Quest Diagnostics)			
<a href="#">Conventional Karyotype Analysis for Pregnancy Loss</a>	Chromosome Analysis, POC, Tissue (Bioreference Labs)	88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291	O03, Z37	1
	Chromosome Analysis, Products of Conception (POC) (GeneDx)			
<a href="#">Exome or Genome Sequencing for Pregnancy Loss</a>	PGxome Prenatal Exome Test (PreventionGenetics)	81415, 81416, 81265, 88235	O03, Z37	13
<a href="#">Prenatal Diagnosis for Single-Gene Disorders</a>	Various Targeted Mutation Analysis	81174, 81177-81190, 81200, 81202, 81204, 81205, 81209,	O26.2, O28, Z14.8	3, 7

		81221, 81239, 81242-81244, 81248, 81250- 81260, 81269, 81271, 81274, 81284-81286, 81289, 81290, 81303, 81312, 81330-81332, 81337, 81343, 81344, 81361- 81364, 81400- 81408, 88235, 81265		
<a href="#">Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies</a>	Prenatal Noonan Spectrum Disorders Panel (GeneDx)	81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235	O28.3, O35.8XX0	8, 10
	Prenatal Noonan Syndrome (LabCorp)			
<a href="#">Prenatal Diagnosis for Skeletal Dysplasias</a>	Prenatal Skeletal Dysplasia Panel (GeneDx)	81404, 81405, 81408, 81479, 81265, 88235	O35.8XX0, O28.3	4
	Skeletal Dysplasia Core NGS Panel (Connective Tissue Gene Tests)			
<a href="#">Prenatal Diagnosis via Exome Sequencing</a>	XomeDx Prenatal-Comprehensive (GeneDx)	81415, 81416, 81265, 88235	O35.8XX0, O28.3	5, 6
	Prenatal Exome Sequencing (Greenwood Genetic Center)			
<a href="#">Prenatal Diagnosis via Genome Sequencing</a>	Prenatal Whole Genome Sequencing	81425, 81426, 81427, 88235, 81265, 0335U, 0336U	O35.8XX0, O28.3	2, 12

## OTHER RELATED POLICIES

This policy document provides coverage criteria for prenatal or pregnancy loss diagnostic testing, and does not address the use of conventional chromosome analysis, CMA, or FISH

for preimplantation genetic testing or the evaluation of suspected chromosome abnormalities in the postnatal period. Please refer to:

- **Genetic Testing: Noninvasive Prenatal Screening (NIPS)** for coverage criteria related to prenatal cell-free DNA screening tests.
- **Genetic Testing: Prenatal and Preconception Carrier Screening** for coverage criteria related to carrier screening for genetic disorders.
- **Genetic Testing: Preimplantation Genetic Testing** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- **Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability and Developmental Delay** for coverage criteria related to suspected chromosome abnormalities in the postnatal period.
- **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.

## COVERAGE CRITERIA

**NOTE:** This policy does not address the use of conventional chromosome analysis, CMA, and FISH for preimplantation genetic testing or the evaluation of suspected chromosome abnormalities in the postnatal period.

## CHROMOSOMAL FISH (ANEUPLOIDY) ANALYSIS

- I. Chromosomal FISH for aneuploidy analysis (81265, 88230, 88235, 88271, 88275, 88291) for prenatal diagnosis via [amniocentesis](#), [CVS](#), or [PUBS](#) may be considered **medically necessary** when:
  - A. The member meets any of the following:
    1. A fetus with one or more major structural abnormalities (see definitions) on ultrasound, **OR**
    2. Advanced maternal age (age greater than or equal to 35 years at delivery), **OR**

3. An abnormal prenatal screening test (e.g., high risk non-invasive prenatal screening, abnormal first trimester or quadruple screen, or antenatal soft markers on ultrasound), **OR**
  4. A parental carrier of a chromosome rearrangement or abnormality, **OR**
  5. Prior pregnancy with a chromosome abnormality, **AND**
- B. The test has been ordered by and the member has received genetic counseling from one of the following (who is not affiliated with the commercial testing laboratory, if applicable):
1. A board-certified medical geneticist
  2. Maternal-fetal medicine specialist/perinatologist
  3. A board-certified OBGYN
  4. A board-certified genetic counselor
  5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology
- II. Chromosomal FISH for aneuploidy analysis (81265, 88230, 88235, 88271, 88275, 88291) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications.

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## CHROMOSOMAL MICROARRAY ANALYSIS (CMA) FOR PRENATAL DIAGNOSIS

- I. Chromosome microarray analysis (81228, 81229, 81265, 88235) 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, 88235) for prenatal diagnosis via [amniocentesis](#), [CVS](#), or [PUBS](#) is considered **investigational** for all other indications.

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## CONVENTIONAL KARYOTYPE ANALYSIS FOR PRENATAL DIAGNOSIS

- I. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) 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 karyotyping via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities.
- II. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications.

**Note:** Current guidelines recommend that chromosome microarray analysis (CMA) be performed as the primary test for patients undergoing prenatal diagnosis when the fetus has one or more major structural abnormalities identified by ultrasound examination (see [Background and Rationale](#) for more information).

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## CHROMOSOMAL MICROARRAY ANALYSIS (CMA) FOR PREGNANCY LOSS

- I. Chromosomal microarray analysis (81228, 81229, 81265, 88235) 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 pregnancy loss at 20 weeks of gestation or earlier and the member has a history of recurrent miscarriage (defined as having two or more failed clinical pregnancies including the current loss), **OR**
  2. The member has a pregnancy loss after 20 weeks of gestation, such as IUFD or stillbirth, **AND**
- B. The test has been ordered by and the member has received genetic counseling from one of the following (who is not affiliated with the commercial testing laboratory, if applicable):
1. A board-certified medical geneticist
  2. Maternal-fetal medicine specialist/perinatologist
  3. A board-certified OBGYN
  4. A board-certified genetic counselor
  5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology
- II. Chromosome microarray analysis (81228, 81229, 81265, 88235) on products of conception (POC) is considered **investigational** for all other indications.

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## CONVENTIONAL KARYOTYPE ANALYSIS FOR PREGNANCY LOSS

- I. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) on products of conception (POC) may be considered **medically necessary** when:
  - A. The member has a history of recurrent miscarriage (defined as having two or more failed clinical pregnancies, including the current loss)
- II. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) on products of conception (POC) is considered **investigational** for all other indications.

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## EXOME OR GENOME SEQUENCING FOR PREGNANCY LOSS

- I. Exome or genome sequencing (81265, 81415, 81416, 88235) for pregnancy loss on products of conception (POC) is considered **investigational**.

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## PRENATAL DIAGNOSIS FOR SINGLE GENE DISORDERS

- I. Prenatal diagnosis for single-gene disorders (81174, 81177-81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242-81244, 81248, 81250-81260, 81269, 81271, 81274, 81284-81286, 81289, 81290, 81303, 81312, 81330-81332, 81337, 81343, 81344, 81361-81364, 81400-81408, 88235, 81265), via amniocentesis, CVS, or PUBS, may be considered **medically necessary** when:
  - A. The member meets any of the following:
    1. At least one biological parent has a known pathogenic variant for an autosomal dominant condition, **OR**
    2. Both biological parents are known carriers of an autosomal recessive condition, **OR**
    3. One biological parent is suspected or known to be a carrier of an X-linked condition, **OR**
    4. The member has a previous affected child with a genetic condition and germline mosaicism is suspected, **AND**
  - B. The natural history of the disease is well-understood, and there is a high likelihood that the disease has high morbidity, **AND**
  - C. The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood, **AND**



- D. The test has been ordered by and the member has received genetic counseling from one of the following (who is not affiliated with the commercial testing laboratory, if applicable):
1. A board-certified medical geneticist
  2. Maternal-fetal medicine specialist/perinatologist
  3. A board-certified OBGYN
  4. A board-certified genetic counselor
  5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology
- II. Prenatal diagnosis for single-gene disorders (81174, 81177-81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242-81244, 81248, 81250-81260, 81269, 81271, 81274, 81284-81286, 81289, 81290, 81303, 81312, 81330-81332, 81337, 81343, 81344, 81361-81364, 81400-81408, 88235, 81265), via amniocentesis, CVS, or PUBS, for adult onset single-gene disorders (examples: hereditary cancer syndromes such as *BRCA1/2*, Huntington disease, etc.) is considered **not medically necessary**.
- III. Prenatal diagnosis for single-gene disorders (81174, 81177-81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242-81244, 81248, 81250-81260, 81269, 81271, 81274, 81284-81286, 81289, 81290, 81303, 81312, 81330-81332, 81337, 81343, 81344, 81361-81364, 81400-81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for variants of unknown significance (VUS).
- IV. Prenatal diagnosis for single-gene disorders (81174, 81177-81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242-81244, 81248, 81250-81260, 81269, 81271, 81274, 81284-81286, 81289, 81290, 81303, 81312, 81330-81332, 81337, 81343, 81344, 81361-81364, 81400-81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for all other indications.

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## PRENATAL DIAGNOSIS FOR NOONAN SPECTRUM DISORDERS/RASOPATHIES

- 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, 88235) may be considered **medically necessary** when:

- A. The member's current pregnancy has had 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 5.0 mm in the first trimester, **OR**
  - 2. The member's current pregnancy has both of the following:
    - a) An increased nuchal translucency of at least 3.5mm, **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.), **AND**
- C. The panel being ordered includes, at a minimum, the following genes: *PTPN11, RAF1, RIT1, SOS1*, **AND**
- D. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, maternal condition), **AND**
- E. The panel has been ordered by and the member has received genetic counseling from one of the following (who is not affiliated with the commercial testing laboratory, if applicable):
  - 1. A board-certified medical geneticist

2. Maternal-fetal medicine specialist/perinatologist
  3. A board-certified OBGYN
  4. A board-certified genetic counselor
  5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology
- 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, 88235) is considered **investigational** for all other indications.

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## PRENATAL DIAGNOSIS FOR SKELETAL DYSPLASIAS

- I. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265, 88235) may be considered **medically necessary** when:
- A. The member's current pregnancy has any of the following 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 member's current pregnancy has had a normal karyotype and/or microarray, **AND**

- C. The panel being ordered includes, at a minimum, the following genes:  
*ALPL, COL1A1, COL1A2, COL2A1, FGFR3, INPPL1, NKX3-2, SLC26A2, SOX9, TRIP11, AND*
- D. The panel has been ordered by and the member has received genetic counseling from one of the following (who is not affiliated with the commercial testing laboratory, if applicable):
  - 1. A board-certified medical geneticist
  - 2. Maternal-fetal medicine specialist/perinatologist
  - 3. A board-certified OBGYN
  - 4. A board-certified genetic counselor
  - 5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology
- II. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265, 88235) is considered **investigational** for all other indications.

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## PRENATAL DIAGNOSIS VIA EXOME SEQUENCING

- I. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265, 88235) may be considered **medically necessary** when:
  - A. The member's current pregnancy has either of the following:
    - 1. Non-immune hydrops fetalis, **OR**
    - 2. Two or more major malformations on ultrasound, which are affecting different organ systems (see definitions), **AND**
  - B. The member's current pregnancy has had a karyotype and/or microarray performed and the results were negative/normal, **AND**
  - C. Alternate etiologies have been considered and ruled out when possible (examples: environmental exposure, injury, infection, maternal condition), **AND**

- D. Postnatal testing may not be feasible due to poor prognosis and increased risk of neonatal demise, **AND**
- E. The panel has been ordered by and the member has received genetic counseling from one of the following (who is not affiliated with the commercial testing laboratory, if applicable):
  - 1. A board-certified medical geneticist
  - 2. Maternal-fetal medicine specialist/perinatologist
  - 3. A board-certified OBGYN
  - 4. A board-certified genetic counselor
  - 5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology
- II. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265, 88235) is considered **investigational** for all other indications.

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## PRENATAL DIAGNOSIS VIA GENOME SEQUENCING

- II. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using genome sequencing (81425, 81426, 81427, 88235, 81265, 0335U, 0336U) is considered **investigational**.

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## NOTES AND DEFINITIONS

- 1. **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
  - Central nervous system: anencephaly, hydrocephalus, myelomeningocele
  - Body wall: omphalocele/gastroschisis
  - Respiratory: cystic adenomatoid lung malformation
2. **Amniocentesis** is a procedure in which a sample of amniotic fluid is removed from the uterus for prenatal diagnostic testing.
  3. **Chorionic Villi Sampling (CVS)** is a procedure where a sample of chorionic villi is removed from the placenta for prenatal diagnostic testing.
  4. **Percutaneous Umbilical Cord Blood Sampling (PUBS)** is a procedure where a sample of fetal blood is extracted from the vein in the umbilical cord.

## CLINICAL CONSIDERATIONS

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).

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## BACKGROUND AND RATIONALE

### Chromosomal FISH (Aneuploidy) Analysis

*American College of Obstetricians and Gynecologists (ACOG)*

An ACOG practice practice bulletin (#162, 2016) states the following:

“Fluorescence in situ hybridization analysis uses fluorescent-labeled probes for specific chromosomes or chromosomal regions to identify the number of those chromosome regions that are present in a specimen. Fluorescence in situ hybridization can be performed on uncultured cells collected by amniocentesis or CVS to provide an assessment of the common aneuploidies...” (p. 3)

“If a patient is at increased risk of having offspring with trisomy 13, 18, or 21 based on abnormal serum screening or cell-free DNA testing, amniocentesis with FISH plus karyotype or with karyotype alone should be offered...” (p. 7)

“If a structural abnormality is strongly suggestive of a particular aneuploidy in the fetus (eg, duodenal atresia or an atrioventricular heart defect, which are characteristic of trisomy 21), karyotype with or without FISH may be offered before chromosomal microarray analysis...” (p. 3)

“An abnormal FISH result should not be considered diagnostic. Therefore, clinical decision making based on information from FISH should include at least one of the following additional results: confirmatory traditional metaphase chromosome analysis or chromosomal microarray, or consistent clinical information (such as abnormal ultrasonographic findings or a positive screening test result for Down syndrome or trisomy 18).” (p. 10-11)

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

*American College of Obstetricians and Gynecologists (ACOG)*

An ACOG practice practice bulletin (#162, 2016) states the 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 (11, 12). 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 (10). If a structural abnormality is strongly suggestive of a particular aneuploidy in the fetus (eg, duodenal atresia or an atrioventricular heart defect, which are characteristic of trisomy 21), karyotype with or without FISH may be offered before chromosomal microarray analysis. (page 3)

- 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 (11), and it is recommended that chromosomal microarray analysis be made available to any patient choosing to undergo invasive diagnostic testing. (page 3)

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

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

A recent 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. 16)

“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. 1)

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### **Chromosomal Microarray Analysis (CMA) for Pregnancy Loss**

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

Because of the advantages chromosomal microarray has over karyotyping (chromosome analysis), ACOG and SMFM support the following for pregnancy loss in their 2016 (reaffirmed 2020) statement:



"Chromosomal microarray analysis of fetal tissue (ie, 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*

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)

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### **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 occurring "after two consecutive clinical pregnancy losses....Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for RPL." (p. 1108 and 1109) For the purposes of this committee, the ASRM defines clinical pregnancy as "...documented by ultrasonography or histopathological examination." (p. 1103)

### **Exome or Genome Sequencing for Pregnancy Loss**

#### *Zhao, C. et al, 2020*

"...this study demonstrated that 22–35% of pregnancy losses have variants of diagnostic value in genes that may contribute to fetal death, supporting the use of Exome Sequencing as a valuable genetic testing tool in searching for a cause for pregnancy loss. The identification of variants of diagnostic value provides necessary information for follow-up parental studies, prenatal genetic counseling, recurrence risk assessment, and

management of subsequent pregnancies. The detection of multiple disease categories and recurrent genes and variants associated with fetal death indicated multiple etiologies for early pregnancy loss. However, further clinicopathologic investigation and functional analysis are needed to determine the cause of fetal death. This could lead to better understanding of the functions of these OMIM genes in fetal development and their roles in pregnancy loss.”(p. 441-442)

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## **Prenatal Diagnosis for Single-Gene Disorders**

### *National Society of Genetic Counselors (NSGC)*

The National Society of Genetic Counselors updated a position statement (2019) regarding prenatal testing for adult-onset conditions, stating the following:

“The National Society of Genetic Counselors (NSGC) does not recommend prenatal genetic testing for known adult-onset conditions if pregnancy or childhood management will not be affected. Due to potential medical and ethical complexities, NSGC recommends that prior to undergoing testing, prospective parents meet with a genetic counselor or other healthcare specialists with genetics expertise to discuss the implications of prenatal testing for adult-onset conditions. Pre-test counseling should include a discussion of the natural history of the condition, availability of treatments or interventions, concerns that prenatal testing for adult-onset conditions may deny a child’s future autonomy, and potential for genetic discrimination.”

### *American College of Obstetricians and Gynecologists (ACOG)*

American College of Obstetricians and Gynecologists (ACOG) practice bulletin 162 (2016) states the following:

“All pregnant women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors.”

Patients with an increased risk of a fetal genetic disorder include those in the following categories: Older maternal age, older paternal age, prior child with structural birth defect, previous fetus or child with autosomal trisomy or sex chromosome aneuploidy, structural anomalies identified by ultrasonography, parental carrier of chromosome rearrangement, parental aneuploidy or aneuploidy mosaicism, parental carrier of a genetic disorder, and biological parent who is affected by an autosomal dominant disorder. (p. 5).

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## Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies

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

This cohort study of ultrasound findings of 424 fetuses in the Netherlands concluded with the recommendation for “testing of fetuses with solely an increased NT after chromosomal abnormalities have been excluded 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 of at least 50% of the fetuses with a rasopathy.” (p. 661)

*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.

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## 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 5th centile or greater than 3 SD below the mean should be evaluated in a center with expertise in the recognition of skeletal dysplasias. If the patient cannot travel, arrangements may be able to be made for evaluation of ultrasound videotapes or hard copy images. (p. 5)
- The following fetal ultrasound measurements should be visualized and plotted against normative values: fetal cranium (biparietal diameter and head circumference), facial profile, mandible, clavicle, scapula, chest circumference, vertebral bodies, all fetal long bones, and the hands and feet. Fetuses with long bone parameters greater than 3 SD below the mean should be strongly suspected of having a skeletal dysplasia, especially if the head circumference is greater than the 75th centile. (p. 5)
- Lethality should be determined by chest circumference to abdominal circumference ratio and/or femur length to abdominal circumference measurement ratio. A chest-to abdominal circumference ratio of  $<0.6$  or femur length to abdominal circumference ratio of 0.16 strongly suggests a perinatal lethal disorder, although there are exceptions. The findings should be conveyed to the physicians caring for the patient and to the patient. (p. 5)

The guidelines also state:

- “Molecular testing should be offered in those pregnancies at-risk for homozygosity or compound heterozygosity for skeletal dysplasias. Both parents’ mutations should have been identified, ideally before pregnancy.” (p. 5)
- “Individuals with skeletal dysplasias known to be due to a number of different mutations should be encouraged to obtain molecular analysis before pregnancy.” (p. 5)
- “In cases where molecular testing is performed and ultrasound findings suggest a lethal prognosis, then counseling should be based on clinical findings and molecular testing should be considered to confirm the clinical findings.” (p. 5)
- “In addition, close attention should be paid to the shape and mineralization pattern of the fetal calvarium and fetal skeleton (poor 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)

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## 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 laboratory report for all tested family members would be reviewed. Both pretest counseling” (p. 676)
- “With the use of prenatal ES, the turnaround time has to be rapid to 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)

*Sparks et al 2020*

A large case series published in the *New England Journal of Medicine* evaluated 127 cases of unexplained nonimmune hydrops fetalis (NIHF) via exome sequencing. (p. 1746) Non-diagnostic karyotype or chromosome microarray was a requirement for eligibility in the study. (p. 1747) Diagnostic genetic variants were found in 29% of cases. (p. 1746) Therefore, the authors conclude with the following: “These data support the use of exome sequencing for NIHF cases with non-diagnostic results of chromosomal microarray analysis or karyotype analysis in order to inform prognosis, establish recurrence risk, and direct prenatal and postnatal clinical care.” (p. 1755)

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## Prenatal Diagnosis Via Whole Genome Sequencing

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

ACOG and SMFM (2016, reaffirmed in 2020) 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 sequencing of fetal DNA obtained by amniocentesis, chorionic villi, or umbilical cord blood is being offered on a research basis in some laboratories and for specific clinical indications in other laboratories. Published data on the prenatal applications of whole-exome sequencing are limited to case series and case reports. However, these series suggest that a genomic abnormality may be identified in up to 20–30% of fetuses with multiple anomalies for which standard genetic testing results (ie, karyotype, microarray, or both) are normal. These cases illustrate how whole-exome sequencing potentially may be used to provide families with a definitive diagnosis, accurate estimates of recurrence risk, and even the options of preimplantation genetic testing or early prenatal diagnosis in a future pregnancy.”

*Zhou J, Yang Z, Sun J, et al. 2021*

“Whole exome sequencing (WES), which detects SNVs, INDELs, and CNVs covering multiple exons, has been proven to be a powerful tool in prenatal diagnosis. In clinical practice, WES can be conducted in CMA-negative cases to further search for single-base lesions. Emerging studies have shown that WES has a detection rate of 8.5% to 10% in fetal structural abnormalities with normal karyotype and CMA results. CMA followed by WES considerably increases the diagnostic yield, and is increasingly accepted as a routine test strategy in clinical practice; however, given the time-sensitive nature of the prenatal stage and the potential inaccessibility of adequate fetal samples, sequential testing is time-consuming and requires a large

amount of DNA as input. More importantly, it is unable to detect certain types of variation, such as balanced translocation or noncoding SNVs/INDELS. Whole genome sequencing (WGS) has the potential to detect almost all types of genomic variants with a low input-DNA requirement ( $\approx 100$  ng) and is proposed to be beneficial in prenatal diagnosis.” (p. 1)

“... 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)

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