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

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.

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).

POLICY REFERENCE TABLE

The tests and associated laboratories and CPT 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 Genetics Platform for a comprehensive list of registered tests.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis	Reveal SNP Microarray - Prenatal (Integrated Genetics)	81228, 81229, 81265, 88235	O26.2, O28, Q00-Q99, Z14.8	3, 9
	Prenatal Whole Genome Chromosomal Microarray (GeneDx)			
Conventional Karyotype Analysis for Prenatal Diagnosis	Chromosome Analysis, Chorionic Villus Sample (Quest Diagnostics)	88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291	O26.2, O28, Q00-Q99, Z14.8	9
	Chromosome Analysis, Amniotic Fluid (Quest Diagnostics)			
Chromosomal Microarray Analysis (CMA) for Pregnancy Loss	SNP Microarray-Products of Conception (POC)/Tissue (Reveal) (Labcorp)	81228, 81229, 81265, 88235	O03, Z37	1, 2, 11
	Chromosomal Microarray, POC, ClariSure Oligo-SNP (Quest Diagnostics)			
Conventional Karyotype Analysis for Pregnancy Loss	Chromosome Analysis, POC, Tissue (Bioreference Labs)	88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291	O03, Z37	1
	Chromosome Analysis, Products of Conception (POC) (ARUP Laboratories)			

Prenatal Diagnosis for Single-Gene Disorders	Various Targeted Mutation Analysis	0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81329, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265	O26.2, O28, Z14.8	3, 7, 14
Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies	Prenatal Noonan Spectrum Disorders Panel (GeneDx) Prenatal Noonan Syndrome (Integrated Genetics)	81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235	O28.3, O35.8XX0	8, 9, 10
Prenatal Diagnosis for Skeletal Dysplasias	Prenatal Skeletal Dysplasia Panel (GeneDx)		O35.8XX0, O28.3	4, 13

	Skeletal Dysplasia Core NGS Panel (Connective Tissue Gene Tests)	81404, 81405, 81408, 81479, 81265, 88235		
Prenatal Diagnosis via Exome Sequencing	XomeDx Prenatal-Comprehensive (GeneDx)	81415, 81416, 81265, 88235	O35.8XX0, O28.3	5, 6
	Prenatal Exome Sequencing (Greenwood Genetic Center)			
Prenatal Diagnosis via Genome Sequencing	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 and Molecular 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.

back to top

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 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.

back to top

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).

back to top

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 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, 88235) on products of conception (POC) is considered **investigational** for all other indications.

back to top

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 pregnancy 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.

back to top

PRENATAL DIAGNOSIS FOR SINGLE GENE DISORDERS

I. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 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 history of a previous child with a genetic condition and the member is suspected to have germline mosaicism, **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.

II. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362,

81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, for adult onset single-gene disorders (examples: hereditary cancer syndromes such as *BRCA1/2,* etc.) is considered **not medically necessary**.

III. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242. 81243, 81244, 81248, 81250-, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284-81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for variants of unknown significance (VUS).

IV. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284-81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for all other indications.

back to top

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 3.0mm, **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, 88235) is considered **investigational** for all other indications.

back to top

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 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, 88235) is considered **investigational** for all other indications.

back to top

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, **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).

II. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265, 88235) is considered **investigational** for all other indications.

back to top

PRENATAL DIAGNOSIS VIA GENOME SEQUENCING

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

back to top

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, fetal growth restriction/intrauterine growth restriction (IUGR)
    - 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.
5. **Recurrent pregnancy loss (RPL)** is defined as having two or more failed clinical pregnancies, including a current loss if applicable

back to top

BACKGROUND AND RATIONALE

Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis

American College of Obstetricians and Gynecologists (ACOG)

An ACOG practice bulletin (#162, 2016, reaffirmed 2020) 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. 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)

back to top

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 chromosomal abnormalities but also the relative benefits and limitations of the available screening and diagnostic tests.” (p. 859)

back to top

Chromosomal Microarray Analysis (CMA) for Pregnancy Loss

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)

back to top

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)

back to top

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, reaffirmed 2020) 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
- Biological parent who is affected by an autosomal dominant disorder. (p. e112-e113)

Some autosomal dominant disorders seen in a previous child but with no other family history may have arisen as a new mutation. In such cases, there may be a small increased risk of recurrence, depending on the disorder. To ensure that any testing for recurrence is informative, a diagnosis established by molecular testing of the affected child usually is necessary. Such confirmation also will ensure that the risk for a future pregnancy has been assessed accurately.

American College of Obstetricians and Gynecologists (ACOG)

ACOG released a committee opinion (no. 693) in April 2017 (reaffirmed 2020) regarding counseling about genetic testing and communication of genetic test results.

The opinion states: “As with any medical test, expectations regarding the performance of a genetic test should be discussed with the patient before the test is ordered. Pretest counseling that includes information on the types of potential results as well as the risks, limitations, and benefits of testing should be provided to all patients before performing any form of genetic test. After counseling, patients should have the option to decline any or all testing.” (p. 1)

A discussion of the sensitivity and specificity of the test for each of the disorders being tested is important to ensure patient understanding. For example, in the case of expanded carrier screening, patients should be informed of the overall range of the carrier detection rate and the range of residual risk of the disorders examined. With reference to each patient’s specific a priori risk, the patient should be informed of the

meaning and significance of positive, negative, or indeterminate test results, as well as results that are normal but may have variable phenotypes. This discussion of the positive predictive value and negative predictive value of the test result facilitates a discussion of the potential need for follow-up diagnostic testing. (p. 3)

back to top

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 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 99th 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.

back to top

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)
- 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)

- 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)

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)

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)

back to top

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." (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)

- 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)

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)

back to top

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 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 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, 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)

back to top

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back to top