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.

POLICY REFERENCE TABLE

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Chromosome FISH (Aneuploidy) Panel	Aneuploidy Panel by FISH, ARUP Laboratories	88271, 88275, 88291, 88235, 81265	O26.2, O28, Q00-Q99, Z14.8	2, 3, 5
Chromosomal Microarray Analysis for Prenatal Diagnosis	Reveal® SNP Microarray - Prenatal, Integrated Genetics	81228, 81229, 88235, 81265	O26.2, O28, Q00-Q99, Z14.8	2, 3
Conventional Chromosome Analysis for Prenatal Diagnosis	Chromosome Analysis - Amniotic Fluid, GeneDx	88261, 88262, 88263, 88264, 88267, 88269, 88235, 81265	O26.2, O28, Q00-Q99, Z14.8	2, 3
Chromosomal Microarray Analysis for Pregnancy Loss	Reveal® SNP Microarray – POC, Integrated Genetics Pregnancy Loss Microarray	81228, 81229, 88235, 81265	O03, Z37	1, 2, 4
Conventional Chromosome Analysis for Pregnancy Loss	Chromosome Analysis - Amniotic fluid	88261, 88262, 88263, 88264, 88267, 88269, 88235, 81265	O03, Z37	1, 2, 4
Prenatal Diagnosis by Exome or Genome Sequencing for Pregnancy Loss		81265, 81266, 81415, 81416, 81417 88235, 81425, 81426	O03, Z37	1, 2
Prenatal Diagnosis for Single-Gene Disorders	Various Targeted Mutation Analysis	81174, 81177-81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242-81244, 81248, 81250-81260, 81269, 81271, 81274,	O26.2, O28, Z14.8	2, 3, 14, 15

		81284-81286, 81289, 81290, 81303, 81312, 81330-81332, 81337, 81343, 81344, 81361-81364, 81400-81408, 88235, 81265		
Prenatal Diagnosis for Noonan Spectrum Disorders/Rasopathies	Prenatal Noonan Spectrum Disorders Panel (GeneDx) Noonan Spectrum Disorders Panel, Sequencing, Fetal (ARUP)	81442, 81265, 81404, 81405, 81406, 81407, 81479, 88235	O28.3, O35.8XX0	2, 9, 10, 16
Prenatal Diagnosis for Skeletal Dysplasias	Prenatal Skeletal Dysplasia Panel (GeneDx) Skeletal Dysplasia Core NGS Panel (Connective Tissue Gene Tests)	81408, 81479, 81443, 81406, 88235	O35.8XX0, O28.3	2, 3, 6, 7, 8
Prenatal Diagnosis via Exome Sequencing	Prenatal Exome Sequencing (Greenwood Genetic Center - Molecular Diagnostic Laboratory) Prenatal Trio Whole Exome Sequencing (Baylor Miraca Genetics Laboratories)	81265, 81266, 81415, 81416, 88235	O35.8XX0, O28.3	2, 11, 12, 17, 18, 19, 20
Prenatal Diagnosis via Whole Genome Sequencing	Diagnostic Genome Sequencing - Trio Auxiliary Family Member (Laboratory for Molecular Medicine - Harvard Medical School and Partners Healthcare)	81425, 81426, 88235, 81265	O35.8XX0, O28.3	2, 13, 19, 20

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 (88271, 88275, 88291, 88235, 81265) 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 ≥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. A member with a 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 (88271, 88275, 88291, 88235, 81265) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications.

back to top

CHROMOSOMAL MICROARRAY ANALYSIS (CMA) FOR PRENATAL DIAGNOSIS

I. Chromosome microarray analysis (81228, 81229, 88235, 81265) 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 ≥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. A 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. Chromosome microarray analysis (81228, 81229, 88235, 81265) 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 (88261, 88262, 88263, 88264, 88267, 88269, 88235, 81265) 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 (maternal age ≥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. A 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. Conventional karyotype analysis (88261, 88262, 88263, 88264, 88267, 88269, 88235, 81265) 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, 88235, 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 pregnancy loss at 20 weeks of gestation or earlier and the member has a history of recurrent miscarriage (defined as having two or more prior failed pregnancies), **OR**

2. The member has a pregnancy loss after 20 weeks of gestation with or without a history of miscarriage, **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, 88235, 81265) 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 (88261, 88262, 88263, 88264, 88267, 88269, 88235, 81265) on products of conception (POC) may be considered **medically necessary** 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 prior failed pregnancies), **OR**

2. The member has a pregnancy loss after 20 weeks of gestation with or without a history of miscarriage, **OR**

B. Chromosomal microarray analysis was previously performed on POC and gave a negative result and the pregnancy was suspected to have a chromosome rearrangement due to a parental balanced chromosomal translocation, **AND**

C. 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. Conventional karyotype analysis (88261, 88262, 88263, 88264, 88267, 88269, 88235, 81265) on products of conception (POC) is considered **investigational** for all other indications.

back to top

PRENATAL DIAGNOSIS USING EXOME OR GENOME SEQUENCING FOR PREGNANCY LOSS

I. Prenatal diagnosis on products of conception (POC) using exome or genome sequencing (81265, 81266, 81415, 81416, 81417, 88235, 81265, 81426) is considered **investigational**.

back to top

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 (e.g., 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.

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 (81442, 88235, 81265) may be considered **medically necessary** when:

A. The member meets one of the following:

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

2. The member's current pregnancy has a heart defect (e.g., pulmonary valve stenosis, atrioventricular septal defect, coarctation of the aorta, hypertrophic cardiomyopathy, atrial septal defect, etc.) and a lymphatic anomaly (e.g., edema, hydrops, pleural effusion, polyhydramnios, etc.) in the second trimester, **AND**

B. The member's current pregnancy has had a normal karyotype and microarray, **AND**

C. The panel being ordered includes, at a minimum, the following genes: *BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, 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 (81442, 88235, 81265) 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 (81408, 81479, 81443, 81406, 88235) may be considered **medically necessary** when:

A. The member's current pregnancy has any of the following ultrasound findings:

1. Long bones <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 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 (81408, 81479, 81443, 81406, 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, 81417, 88235, 81265) 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 microarray performed and the results were negative/normal, **AND**

C. Alternate etiologies have been considered and ruled out when possible (e.g., 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, 81417, 88235, 81265) is considered **investigational** for all other indications.

back to top

PRENATAL DIAGNOSIS USING GENOME SEQUENCING

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

back to top

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).

back to top

BACKGROUND AND RATIONALE

Practice Guidelines and Committee Statements

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

ACOG and SMFM (2016) 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:

- "Chromosomal microarray analysis is a method of measuring gains and losses of DNA throughout the human genome. It can identify chromosomal aneuploidy and other large changes in the structure of chromosomes that would otherwise be identified by standard karyotype analysis, as well as submicroscopic abnormalities that are too small to be detected by traditional modalities."
- "Most genetic changes identified by chromosomal microarray analysis that typically are not identified on standard karyotype are not associated with increasing maternal age; therefore, the use of this test can be considered for all women, regardless of age, who undergo prenatal diagnostic testing."
- "Prenatal chromosomal microarray analysis is recommended for a patient with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who is undergoing invasive prenatal diagnosis. This test typically can replace the need for fetal karyotype."
- "In a patient with a structurally normal fetus who is undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed."
- "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."
- "Comprehensive patient pretest and posttest genetic counseling from an obstetrician–gynecologist or other health care provider with genetics expertise regarding the benefits, limitations, and results of chromosomal microarray analysis is essential."
- "Chromosomal microarray analysis should not be ordered without informed consent, which should include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease."

- "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."

ACOG and SMFM (2016) published the joint practice bulletin No. 162 and made the following considerations and recommendations regarding prenatal diagnostic testing for genetic disorders:

The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- "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 result and a normal karyotype, and it is recommended that chromosomal microarray analysis be made available to any patient choosing to undergo invasive diagnostic testing."
- "Early amniocentesis (before 14 weeks of gestation) is not recommended."
- "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. 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."

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- "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)."

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- "All pregnant women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors."
- "Prenatal genetic testing cannot identify all abnormalities or problems in a fetus, and any testing should be focused on the individual patient's risks, reproductive goals, and preferences."
- "Genetic testing should be discussed as early as possible in pregnancy, ideally at the first obstetric visit, so that first-trimester options are available."

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 the following conclusions:

- "Evaluation of recurrent pregnancy loss can proceed after 2 consecutive clinical pregnancy losses."
- "Assessment of recurrent pregnancy loss focuses on screening for genetic factors and antiphospholipid syndrome, assessment of uterine anatomy, hormonal and metabolic factors, and lifestyle variables. These may include:
    - Peripheral karyotype of the parents.
    - Screening for lupus anticoagulant, anticardiolipin antibodies, and anti-β_2 glycoprotein I.
    - Sonohysterogram, hysterosalpingogram, and/or hysteroscopy.
    - Screening for thyroid and prolactin abnormalities."
- "Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for recurrent pregnancy loss."

American College of Medical Genetics and Genomics

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."

- "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"
- "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."
- "Post-test counseling is recommended, regardless of the test result. It should be provided by individuals with relevant expertise, preferably a genetics professional."

ACMG issued guidelines for the prenatal diagnosis of fetal skeletal dysplasias (2009) that included the following recommendations:

- "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."
- "Individuals with skeletal dysplasias known to be due to a number of different mutations should be encouraged to obtain molecular analysis before pregnancy."
- "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."

National Society of Genetic Counselors (NSGC)

The National Society of Genetic Counselors updated a position statement (2017) regarding the genetic testing of minors for adult-onset conditions, stating the following:

> "[NSGC] encourages deferring predictive genetic testing of minors for adult-onset conditions when results will not impact childhood medical management or significantly benefit the child. Predictive testing should optimally be deferred until the individual has the capacity to weigh the associated risks, benefits, and limitations of this information, taking his/her circumstances, preferences, and beliefs into account to preserve his/her autonomy and right to an open future."

Huntington's Disease Society of America

Huntington's Disease Society of America published a protocol for genetic testing for Huntington's disease (2016) which include the following statements on prenatal testing for HD:

- "Individuals or couples considering prenatal testing are advised to seek genetic counseling prior to a pregnancy. Many reproductive options are available to Individuals affected by or at risk for HD, of which prenatal testing is one. Samples for prenatal analysis of the HD gene may be obtained in two ways: by chorionic villus sampling at 10-12 weeks of pregnancy, or by amniocentesis at 14-20 weeks. Some couples may also desire preimplantation testing of a fertilized embryo. This requires the use of fertility drugs and other procedures available only at specialized in vitro fertilization centers."
- "Chorionic Villus Sampling (CVS) is offered at some clinics for women from their 10th through 12th weeks of pregnancy. Amniocentesis can be done from the 14th through 20th weeks of pregnancy. This process includes genetic counseling to explore the parents' questions and concerns and to educate them about the risks involved. It is important for parents to explore what they hope to gain from this procedure, especially if they are not planning to terminate the pregnancy. As with testing of asymptomatic minors, CVS and Amniocentesis take away the child's option not to know his or her gene status."
- "CVS and Amniocentesis can be done if a parent is at risk or if he or she has tested positive for the gene that causes HD. If a parent has decided not to test, then genetic counseling must include the impact for both the parents and child of getting a positive result for the fetus. Testing the fetus when a parent does not want to know his/her own gene status can lead to a difficult situation wherein the at-risk parent will come to know his or her genetic status as a result of the fetal test. These instances require careful consideration."

back to top

REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103-1111. doi:10.1016/j.fertnstert.2012.06.048

2. Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. Obstet Gynecol. 2016;128(6):e262-e268. doi:10.1097/AOG.0000000000001817
3. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal–Fetal Medicine. Practice Bulletin No. 162: Prenatal Diagnostic Testing for Genetic Disorders. Obstet Gynecol. 2016;127(5):e108-e122. doi:10.1097/AOG.0000000000001405
4. Sahoo T, Dzidic N, Strecker MN, et al. Comprehensive genetic analysis of pregnancy loss by chromosomal microarrays: outcomes, benefits, and challenges. Genet Med. 2017;19(1):83-89. doi:10.1038/gim.2016.69
5. Test and Technology Transfer Committee, American College of Medical Genetics, 9650 Rockville Pike, Bethesda, MD 20814-3998, United States.. Technical and clinical assessment of fluorescence in situ hybridization: an ACMG/ASHG position statement. I. Technical considerations. Test and Technology Transfer Committee. Genet Med. 2000;2(6):356-361. doi:10.1097/00125817-200011000-00011
6. Zhou X, Chandler N, Deng L, Zhou J, Yuan M, Sun L. Prenatal diagnosis of skeletal dysplasias using a targeted skeletal gene panel. Prenat Diagn. 2018;38(9):692-699. doi:10.1002/pd.5298
7. Krakow D, Lachman RS, Rimoin DL. Guidelines for the prenatal diagnosis of fetal skeletal dysplasias. Genet Med. 2009;11(2):127-133. doi:10.1097/GIM.0b013e3181971ccb
8. Mortier GR, Cohn DH, Cormier-Daire V, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. Am J Med Genet A. 2019;179(12):2393-2419. doi:10.1002/ajmg.a.61366
9. Leach NT, Wilson Mathews DR, Rosenblum LS, Zhou Z, Zhu H, Heim RA. Comparative assessment of gene-specific variant distribution in prenatal and postnatal cohorts tested for Noonan syndrome and related conditions [published correction appears in Genet Med. 2018 Jul 26;:]. Genet Med. 2019;21(2):417-425. doi:10.1038/s41436-018-0062-0
10. Leach NT, Wilson Mathews DR, Rosenblum LS, Zhou Z, Zhu H, Heim RA. Correction: Comparative assessment of gene-specific variant distribution in prenatal and postnatal cohorts tested for Noonan syndrome and related conditions. Genet Med. 2019;21(7):1670. doi:10.1038/s41436-018-0128-z
11. Monaghan KG, Leach NT, Pekarek D, Prasad P, Rose NC; ACMG Professional Practice and Guidelines Committee. The use of fetal exome sequencing in prenatal

diagnosis: a points to consider document of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(4):675-680. doi:10.1038/s41436-019-0731-7

12. Sparks TN, Lianoglou BR, Adami RR, et al. Exome Sequencing for Prenatal Diagnosis in Nonimmune Hydrops Fetalis [published online ahead of print, 2020 Oct 7]. N Engl J Med. 2020;10.1056/NEJMoa2023643. doi:10.1056/NEJMoa2023643
13. Donley G, Hull SC, Berkman BE. Prenatal whole genome sequencing: just because we can, should we?. Hastings Cent Rep. 2012;42(4):28-40. doi:10.1002/hast.50
14. "Prenatal Testing for Adult-Onset Condition". Position Statement from National Society for Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/prenatal-testing-for-adult-onset-conditions-1. Released October 9, 2018. Updated June 26, 2019.
15. "Genetic Testing Protocol for Huntington's Disease". Huntington's Disease Society of America. http://hdsa.org/wp-content/uploads/2015/02/HDSA-Gen-Testing-Protocol-for-HD.pdf. 2016. Accessed October 27, 2020.
16. Stuurman KE, Joosten M, van der Burgt I, et al. Prenatal ultrasound findings of rasopathies in a cohort of 424 fetuses: update on genetic testing in the NGS era. J Med Genet. 2019;56(10):654-661. doi:10.1136/jmedgenet-2018-105746
17. Tolusso LK, Hazelton P, Wong B, Swarr DT. Beyond diagnostic yield: prenatal exome sequencing results in maternal, neonatal, and familial clinical management changes [published online ahead of print, 2021 Jan 13]. Genet Med. 2021;1-9. doi:10.1038/s41436-020-01067-9
18. Pratt M, Garritty C, Thuku M, et al. Application of exome sequencing for prenatal diagnosis: a rapid scoping review. Genet Med. 2020;22(12):1925-1934. doi:10.1038/s41436-020-0918-y
19. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement o the American College of Medical Genetics and Genomics (ACMG) [published online ahead of print, 2021 May 20]. Genet Med. 2021;10.1038/s41436-021-01171-4. doi:10.1038/s41436-021-01171-4
20. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG) [published online ahea

of print, 2021 May 20]. Genet Med. 2021;10.1038/s41436-021-01172-3. doi:10.1038/s41436-021-01172-3

back to top