Medica Central Coverage Policy

Policy Name:	**Genetic Testing - Reproductive Testing: Prenatal Diagnosis**
Effective Date:	**01/01/2026**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

OVERVIEW

This policy addresses the use of tests for genetic disorders during pregnancy and following a pregnancy loss. These tests may be used to identify genetic conditions in fetuses determined to be at an increased risk for a genetic disorder.

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 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.

For additional information see the Rationale and References section.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage. Please see the Concert Platform for additional registered tests.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Broad Prenatal Diagnosis Testing			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis	Reveal SNP Microarray - Prenatal (Integrated Genetics)	81228, 81229, 81265, 88235, 81349, 81479, 0469U, O26.2, O28, Q00-Q99, Z14.8	Rationale/ References
	Prenatal Whole Genome Chromosomal Microarray (GeneDx)		
	IriSight CNV Analysis - 0469U (Variantyx)		
	CNGnome NGS Array (Revvity)		
Conventional Karyotype Analysis for Prenatal Diagnosis	Chromosome Analysis, Chorionic Villus Sample (Quest Diagnostics)	88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88289, 88291, O26.2, O28, Q00-Q99, Z14.8	Rationale/ References
	Chromosome Analysis, Amniotic Fluid (Quest Diagnostics)		
Prenatal Diagnosis via Exome Sequencing	XomeDx Prenatal - Comprehensive (GeneDx)	81415, 81416, 81265, 88235, O35.8XX0, O28.3	Rationale/ References
	Prenatal Exome Sequencing (Greenwood Genetic Center - Molecular Diagnostic Laboratory)		
Prenatal Diagnosis via Genome Sequencing	Prenatal Whole Genome Sequencing	81425, 81426, 88235, 81265, 0335U, 0336U, 0532U, O35.8XX0, O28.3	Rationale/ References
	IriSight Prenatal Analysis - Proband - 0335U (Variantyx)		
	IriSight Prenatal Analysis - Comparator - 0336U (Variantyx)		
	Rapid Genome Sequencing Test - 0532U (University of California		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	San Francisco Genomic Medicine Laboratory)		
Pregnancy Loss Testing			
Chromosomal Microarray Analysis (CMA) for Pregnancy Loss	SNP Microarray-Products of Conception (POC)/Tissue (Reveal) (LabCorp)	81228, 81229, 81265, 88235, 81349, 81479, O03, Z37	Rationale/ References
	Chromosomal Microarray, POC, ClariSure Oligo-SNP (Quest Diagnostics)		
	CNGnome NGS Array (Revvity)		
Conventional Karyotype Analysis for Pregnancy Loss	Chromosome Analysis, POC, Tissue (Bioreference Laboratories)	88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291, O03, Z37	Rationale/ References
	Chromosome Analysis, Products of Conception (POC) (ARUP Laboratories)		
Targeted Prenatal Diagnosis Testing			
Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies	Prenatal Noonan Spectrum Disorders Panel (GeneDx)	81404, 81405, 81406, 81407, 81442, 81479, 81265, 88235, O28.3, O35.8XX0	Rationale/ References
	Prenatal Noonan Syndrome (Integrated Genetics)		
Prenatal Diagnosis for Skeletal Dysplasias	Prenatal Skeletal Dysplasia Panel (GeneDx)	81404, 81405, 81408, 81479, 81265, 88235, O35.8XX0, O28.3	Rationale/ References
	Skeletal Dysplasia Core NGS Panel (HNL Genomics)		

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:

- ***Reproductive Testing: Prenatal Screening*** for coverage criteria related to fetal screening for genetic disorders during pregnancy.
- ***Reproductive Testing: Carrier Screening*** for coverage criteria related to parental carrier screening for genetic disorders before or during pregnancy.
- ***Reproductive Testing: Fertility*** for coverage criteria related to preimplantation diagnosis.
- ***Specialty Testing: Multisystem Genetic Conditions*** for coverage criteria related to diagnostic tests for genetic disorders that affect multiple organ systems (e.g., whole exome and genome sequencing, chromosomal microarray, and multigene panels for broad phenotypes).
- ***General Approach to Laboratory Testing*** for coverage criteria related to reproductive genetic testing, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

BROAD PRENATAL DIAGNOSIS TESTING

Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis

I. Chromosome microarray analysis 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, **AND**

   B. The member is NOT simultaneously undergoing karyotype analysis.

II. Chromosome microarray analysis 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 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 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 members undergoing prenatal diagnosis when the fetus has one or more major structural abnormalities identified by ultrasound examination.

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Prenatal Diagnosis via Exome Sequencing

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

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

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

   C. 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.

II. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing is considered **investigational** for all other indications.

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Prenatal Diagnosis via Genome Sequencing

I. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using genome sequencing is considered **investigational** for all indications.

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PREGNANCY LOSS TESTING

Chromosomal Microarray Analysis (CMA) for Pregnancy Loss

I. Chromosomal microarray analysis 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 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 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 on products of conception (POC) is considered **investigational** for all other indications.

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TARGETED PRENATAL DIAGNOSIS TESTING

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 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 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 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 is considered **investigational** for all other indications.

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RATIONALE AND REFERENCES

Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis

American College of Obstetricians and Gynecologists (ACOG)

ACOG practice bulletin no. 162 (2016, reaffirmed 2020 and 2024) states the following:

- Chromosomal microarray is recommended to be offered to "any patient choosing to undergo invasive diagnostic testing" (p. e117)
- Chromosome microarray is recommended "as the primary test (replacing conventional karyotype)" when fetal structural abnormalities are detected by ultrasound examination (p. e117)
- In fetuses with signs and suggestive features of a specific aneuploidy, "karyotype with or without FISH may be offered before chromosomal microarray" (p. e117).

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 (Reaffirmed 2020 and 2024);127(5):e108-e122. doi:10.1097/AOG.0000000000001405

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

The joint ACOG-SMFM committee opinion no. 682 (2016, reaffirmed 2020 and 2023) recommends that prenatal chromosome microarray analysis (CMA) be performed for a fetus with one or more structural anomalies, and this test can replace the need for fetal karyotype (p. 1). They also state that in a structurally normal fetus, either fetal karyotyping or CMA can be performed if the patient is undergoing invasive prenatal diagnostic testing (p. 1-2).

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

ACOG practice bulletin no. 226 (2020, reaffirmed 2024) 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).

American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020 (Reaffirmed

2024);136(4):859-867. doi:10.1097/AOG.0000000000004084

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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 no.226 (2020, reaffirmed 2024) recommends screening and diagnostic testing be offered to all pregnant women, "regardless of maternal age or risk of chromosomal abnormality". Diagnostic testing includes chorionic villus sampling [CVS] or amniocentesis (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).

American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020 (Reaffirmed 2024);136(4):859-867. doi:10.1097/AOG.0000000000004084

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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" (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).

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

Al-Kouatly, et al.

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

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

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

Al-Kouatly HB, Shivashankar K, Mossayebi MH, et al. Diagnostic yield from prenatal exome sequencing for non-immune hydrops fetalis: a systematic review and meta-analysis. Clin Genet. 2023;103(5):503-512. doi:10.1111/cge.14309

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Prenatal Diagnosis via Genome Sequencing

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

ACOG and SMFM (2016, reaffirmed in 2020 and 2023) issued a committee opinion no. 682, which included the following conclusions and recommendations for the use of chromosomal microarray testing and next-generation sequencing in prenatal diagnosis.

Note that while whole exome sequencing is addressed in this opinion, whole genome sequencing is not yet recommended:

“Whole-exome sequencing also is a broad molecular diagnostic approach to identify the etiology for fetal abnormalities, and whole-exome 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. However, the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis is not recommended outside of the context of clinical trials until sufficient peer-reviewed data and validation studies are published ” (p. 4).

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

International Society for Prenatal Diagnosis (ISPD)

ISPD issued a position statement in 2022 regarding the use of genome-wide sequencing for prenatal diagnosis. They do not recommend routine use of prenatal exome or genome sequencing as a diagnostic test due to lack of sufficient evidence for clinical validity (p. 10).

Van den Veyver IB, Chandler N, Wilkins-Haug LE, Wapner RJ, Chitty LS; ISPD Board of Directors. International Society for Prenatal Diagnosis Updated Position Statement on the use of genome-wide sequencing for prenatal diagnosis. Prenat Diagn. 2022;42(6):796-803. doi:10.1002/pd.6157

Zhou J, et al.

An article by Zhou, et al. prospectively evaluated the clinical utility of whole genome sequencing (WGS) compared with standard chromosome microarray (CMA) in fetuses with structural

anomalies. WGS was found to have a diagnostic rate of 19.8%, and was able to provide additional clinical information, such as a balanced translocation.

The article concludes by saying that “with a rapid TAT, good diagnostic yield, and less DNA required, WGS could be an alternative test in lieu of two separate analyses as it has an equivalent diagnostic yield to that of CMA plus WES and provides comprehensive detection of various genomic variants in fetuses with structural or growth anomalies. However, more prospective studies with larger cohorts and further evaluation are warranted to demonstrate the value of WGS in prenatal diagnosis” (p. 12).

Zhou J, Yang Z, Sun J, et al. Whole Genome Sequencing in the Evaluation of Fetal Structural Anomalies: A Parallel Test with Chromosomal Microarray Plus Whole Exome Sequencing. Genes. 2021; 12(3):376. https://doi.org/

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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)

The ACOG and SMFM practice bulletin no. 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).

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

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).

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

Papas, et al.

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).

Papas RS, Kutteh WH. Genetic testing for aneuploidy in patients who have had multiple miscarriages: a review of current literature. Appl Clin Genet. 2021;14:321-329.

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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 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).

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

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Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies

Stuurman, et al.

This 2019 cohort study of ultrasound findings of 424 fetuses in the Netherlands concluded with the recommendation to test fetuses with isolated increased NT (nuchal translucency) when the NT is greater than or equal to 5.0 mm, after a normal karyotype has been established. The authors also recommend testing when NT is greater than or equal to 3.5 mm and in the presence of at least one of the following anomalies: distended jugular lymph sacs (JLS), hydrops fetalis, polyhydramnios, pleural effusion and cardiac defects (p. 660).

If a RASopathy is suspected, the authors recommend testing via an NGS panel of known RASopathy genes. While the authors acknowledge that PTPN11 testing alone would detect at least 50% of fetuses with a RASopathy, it is still preferable to perform a panel (if available), as affected fetuses with pathogenic variants in a variety of RASopathy genes are documented in the literature (p. 661).

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

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

The ACOG and SMFM practice bulletin no. 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).

American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020 (Reaffirmed 2024);136(4):859-867. doi:10.1097/AOG.0000000000004084

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.

Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2022 Feb 17]. In: Adam MP, Mirzaa MP, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/

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Prenatal Diagnosis for Skeletal Dysplasias

Krakow, et al.

A guideline for prenatal diagnosis of fetal skeletal dysplasias (2009) recommends the following 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. (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 guideline also lists several other common abnormal ultrasound findings in Table 2, including fractures of long bones (primarily femora), poor mineralization of the vertebrae, bent/bowed legs, and absent/hypoplastic scapula, as additional ultrasound findings that would prompt evaluation. (p. 10)

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

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).

Scocchia A, Kangas-Kontio T, Irving M, et al. Diagnostic utility of next-generation sequencing-based panel testing in 543 patients with suspected skeletal dysplasia. Orphanet J Rare Dis. 2021;16:412. doi:10.1186/s13023-021-02025-7

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DEFINITIONS

1. **Amniocentesis** is a procedure in which a sample of amniotic fluid is removed from the uterus for prenatal diagnostic testing.
2. **Chorionic Villi Sampling (CVS)** is a procedure where a sample of chorionic villi is removed from the placenta for prenatal diagnostic testing.
3. **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

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.

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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

	Committee/Source	Date(s)
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