# Concert Genetic Testing: Prenatal Diagnosis ~~(Via Amniocentesis, CVS, Or PUBS) and Pregnancy Loss~~

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Revision Log

Coding implications

**See** Important Reminder **at the end of this policy for important regulatory and legal information.**

## 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). Exome and genome sequencing are also emerging as new prenatal diagnostic tools.~~

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~~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).~~

For additional information see the Rationale 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

**Coding Implications**

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted ~~2023~~2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests, ~~associated laboratories,~~ CPT codes, and ICD codes ~~contained within~~referenced in this ~~document serve only as examples to help users navigate claims and corresponding criteria; as such, they~~policy are not comprehensive, and ~~are~~their inclusion does not represent a guarantee of coverage or non-coverage. Please see the ~~Concert Platform~~Concert Platform for ~~a comprehensive list of~~additional registered tests.

**NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.**

| ~~Criteria Sections~~CRITERIA SECTIONS | ~~Example Tests (Labs)~~EXAMPLE TESTS (LABS) | ~~Common CPT Codes~~COMMON BILLING CODES | ~~Common ICD Codes~~RE | ~~Ref~~ |
|---|---|---|---|---|

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| | | | | F | |
| **Broad Prenatal Diagnosis Testing** | | | | | |
| ~~Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis~~Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis | Reveal SNP Microarray - Prenatal (Integrated Genetics) | 81228*, 81229, 81265, 88235, 0469U*, O26.2, O28, Q00-Q99, Z14.8 | ~~O26.2, O28, Q00-Q99, Z14.8~~ | 3, 7 | |
| | | | | | |
| | Prenatal Whole Genome Chromosomal Microarray (GeneDx) | | | | |
| | | ~~0469U*~~ | | | |
| | IriSight CNV Analysis - 0469U (Variantyx) | | | | |
| | | | | | |
| ~~Conventional Karyotype Analysis for Prenatal Diagnosis~~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 | ~~O26.2, O28, Q00-Q99, Z14.8~~ | 7 | |
| | | | | | |

| | | | | |
|---|---|---|---|---|
| | Chromosome Analysis, Amniotic Fluid (Quest Diagnostics) | | | |
| Prenatal Diagnosis via Exome Sequencing | XomeDx Prenatal - Comprehensive (GeneDx)<br>Prenatal Exome Sequencing (Greenwood Genetic Center - Molecular Diagnostic Laboratory) | 81415*, 81416*, 81265, 88235, O35.8XX0, O28.3 | | 5, 12 |
| Prenatal Diagnosis via Genome Sequencing | Prenatal Whole Genome Sequencing<br>IriSight Prenatal Analysis - 0335U (Variantyx) | 81425, 81426, 88235, 81265, 0335U, 0336U, O35.8XX0, O28.3 | | 2, 10 |
| **Pregnancy Loss Testing** | | | | |
| ~~Chromosomal Microarray Analysis (CMA) for Pregnancy Loss~~<br>Chromosomal Microarray Analysis (CMA) for Pregnancy Loss | SNP Microarray-Products of Conception (POC)/Tissue (Reveal) (Labcorp) | 81228*, 81229, 81265, 88235~~-~~, O03, Z37 | ~~O03, Z37~~ | 1, 2, 9 |
| | Chromosomal Microarray, POC, ClariSure Oligo-SNP (Quest Diagnostics) | | | |
| ~~Conventional Karyotype Analysis for Pregnancy Loss~~Conventional Karyotype Analysis for | Chromosome Analysis, POC, | 88235, 88261, | ~~O03, Z37~~ | 1 |

| | | | | |
|---|---|---|---|---|
| Pregnancy Loss | Tissue (Bioreference Labs) | 88262, 88263, 88264, 88267, 88269, 88280, 88291~~-~~, O03, Z37 | | |
| | Chromosome Analysis, Products of Conception (POC) (ARUP Laboratories) | | | |
| **Targeted Prenatal Diagnosis Testing** | | | | |
| ~~Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies~~Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies | Prenatal Noonan Spectrum Disorders Panel (GeneDx) | 81404*, 81405*, 81406*, 81407*, 81479, 81442*, 81265, 88235, O28.3, O35.8XX0 | ~~O28.3~~, ~~O35.8XX0~~ | 6, 7, 8 |
| | Prenatal Noonan Syndrome (Integrated Genetics) | | | |
| ~~Prenatal Diagnosis for Skeletal Dysplasias~~Prenatal Diagnosis for Skeletal Dysplasias | Prenatal Skeletal Dysplasia Panel (GeneDx) | 81404*, 81405*, 81408*, 81479, 81265, 88235, | ~~O35.8XX0, O28.3~~ | 4, 11 |

| | | | | |
|---|---|---|---|---|
| | | O35.8XX0, O28.3 | | |
| | Skeletal Dysplasia Core NGS Panel (Connective Tissue Gene Tests) | | | |
| ~~Prenatal Diagnosis via Exome Sequencing~~ | ~~XomeDx Prenatal – Comprehensive (GeneDx)~~ | ~~81415*, 81416*, 81265, 88235~~ | ~~O35~~ | |
| | ~~Prenatal Exome Sequencing (Greenwood Genetic Center – Molecular Diagnostic Laboratory)~~ | | | |
| ~~Prenatal Diagnosis via Genome Sequencing~~ | ~~Prenatal Whole Genome Sequencing~~ | ~~81425, 81426, 81427, 88235, 81265~~ | ~~O35~~ | |
| | ~~IriSight Prenatal Analysis (Varianty x)~~ | ~~0335U*, 0336U*~~ | | |

# ~~OTHER~~ RELATED POLICIES

This policy document provides 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***~~***Reproductive Testing: Prenatal*** ~~***Cell-free DNA***~~***Screening*** for criteria related to fetal screening for genetic disorders during pregnancy.
- ~~***Reproductive Testing*** for criteria related to prenatal cell-free DNA screening tests.~~
- ~~***Genetic Testing: Prenatal and Preconception:***~~ ***Carrier Screening*** for criteria related to parental carrier screening for genetic disorders before or during pregnancy.
- ~~***Genetic***~~***Reproductive Testing:*** ~~***Preimplantation Genetic Testing***~~***Fertility*** for criteria related to ~~genetic testing of embryos prior to in vitro fertilization.~~ preimplantation diagnosis.
- ~~***Genetic***~~***Specialty Testing: Multisystem*** ~~***Inherited Disorders, Intellectual Disability and Developmental Delay***~~***Genetic Conditions*** for criteria related to ~~suspected chromosome abnormalities in the postnatal period.~~ 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).
- ~~***Genetic Testing:***~~ ***General Approach to*** ~~***Genetic and Molecular***~~***Laboratory Testing*** for criteria related to ~~prenatal diagnostic or pregnancy loss~~reproductive genetic testing, including known familial variant testing, that is not specifically discussed in this or ~~other~~another non-general ~~policies, including known familial variant testing~~policy.

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# CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is **medically necessary** when meeting the related 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~~BROAD PRENATAL DIAGNOSIS TESTING

## Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis

I. Chromosome microarray analysis ~~(81228, 81229, 81265, 88235, 0469U)~~ for prenatal diagnosis via ~~amniocentesis, CVS, or PUBS~~amniocentesis, CVS, or PUBS may be considered **medically necessary** when:

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

II. ~~Chromosome~~Current evidence does not support chromosome microarray analysis ~~(81228, 81229, 81265, 88235, 0469U)~~ for prenatal diagnosis via ~~amniocentesis, CVS, or PUBS is considered **investigational**~~amniocentesis, CVS, or PUBS for all other indications.

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## ~~CONVENTIONAL KARYOTYPE ANALYSIS FOR PRENATAL DIAGNOSIS~~

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## Conventional Karyotype Analysis for Prenatal Diagnosis

I. Conventional karyotype analysis ~~(88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) for~~ for prenatal diagnosis via ~~amniocentesis, CVS, or PUBS~~ amniocentesis, CVS, or PUBS may be considered **medically necessary** when:

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

II. ~~Conventional~~Current evidence does not support conventional karyotype analysis ~~(88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291)~~ for prenatal diagnosis via ~~amniocentesis, CVS, or PUBS is considered **investigational**~~amniocentesis, CVS, or PUBS for all other indications.

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

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## 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/enrollee'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/enrollee's current pregnancy has either of the following:

1. Non-immune hydrops fetalis, **OR**

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2. ~~CHROMOSOMAL MICROARRAY ANALYSIS (CMA) FOR~~ Two or more major malformations on ultrasound, which are affecting different organ systems.

II. Current evidence does not support prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing for all other indications.

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## Prenatal Diagnosis via Genome Sequencing

I. Current evidence does not support prenatal diagnosis, via amniocentesis, CVS, or PUBS, using genome sequencing 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/enrollee meets one of the following:

~~I. (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/enrollee meets one of the following:~~

1. The member/enrollee has a history of ~~recurrent pregnancy loss~~recurrent pregnancy loss, **OR**

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

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

~~1. The member/enrollee has a pregnancy loss at or greater than 20 weeks of gestation (i.e., IUFD or stillbirth), **AND**~~

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

II. ~~Chromosome~~Current evidence does not support chromosome microarray analysis ~~(81228, 81229, 81265, 88235)~~ on products of conception (POC) ~~is considered **investigational**~~ for all other indications.

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## ~~CONVENTIONAL KARYOTYPE ANALYSIS FOR PREGNANCY LOSS~~

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## Conventional Karyotype Analysis for Pregnancy Loss

I. Conventional karyotype analysis ~~(88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291)~~ on products of conception (POC) may be considered **medically necessary** when:

   A. The member/enrollee has a history of ~~recurrent pregnancy loss~~recurrent pregnancy loss.

II. ~~Conventional~~Current evidence does not support conventional karyotype analysis ~~(88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291)~~ on products of conception (POC) ~~is considered **investigational**~~ for all other indications.

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## TARGETED PRENATAL DIAGNOSIS ~~FOR NOONAN SPECTRUM DISORDERS/RASOPATHIES~~TESTING

## Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies

I. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via ~~amniocentesis, CVS, or PUBS,~~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/enrollee's current pregnancy has had a normal karyotype and/or microarray, **AND**

   B. The member/enrollee meets one of the following:

      1. The member/enrollee'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/enrollee'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~~ Current evidence does not support prenatal diagnosis for Noonan spectrum disorders/RASopathies, via ~~amniocentesis, CVS, or PUBS~~amniocentesis, CVS, or PUBS, using a Noonan syndrome panel ~~(81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235) is considered **investigational**~~ for all other indications.

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## ~~PRENATAL DIAGNOSIS FOR SKELETAL DYSPLASIAS~~

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## Prenatal Diagnosis for Skeletal Dysplasias

I. Prenatal diagnosis for skeletal dysplasias, via ~~amniocentesis, CVS, or PUBS~~amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel ~~(81404, 81405, 81408, 81479, 81265, 88235)~~ may be considered **medically necessary** when:

A. The member/enrollee'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~~Current evidence does not support prenatal diagnosis for skeletal dysplasias, via ~~amniocentesis, CVS, or PUBS~~amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel ~~(81404, 81405, 81408, 81479, 81265, 88235) is considered **investigational**~~ for all other indications.

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## ~~PRENATAL DIAGNOSIS VIA EXOME SEQUENCING~~

~~I. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265, 88235) may be considered **medically necessary** when:~~

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

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

~~C.~~~~A.~~ ~~The member/enrollee'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 (81415, 81416, 81265, 88235) 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 (81425, 81426, 81427, 88235, 81265, 0335U, 0336U) is considered **investigational**.~~

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# 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

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BACKGROUND AND view rationale

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# 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~~)~~).

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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 (#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~~)~~).

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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 (#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)~~

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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)

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## Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies

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

This cohort study of ultrasound findings of 424 fetuses in the Netherlands concluded with the recommendation for "testing of fetuses with solely an increased NT after chromosomal abnormalities have been excluded when the NT is greater than or equal to 5.0 mm. We also recommend testing when the NT is greater than or equal to 3.5 mm and at least one of the following anomalies is present: distended jugular lymph sacs (JLS), hydrops fetalis, polyhydramnios, pleural effusion and cardiac defects." (p. 660)

"In general, an NGS panel of known rasopathy genes should be used when a rasopathy is suspected. Although we did not find pathogenic variants in every gene in the panel, in all genes, a prenatal phenotype has been documented in literature. Therefore, a smaller panel is not advisable. However, in countries where an extensive panel is not available, testing for only *PTPN11* gene would catch 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.

## 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. (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)

*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)

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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~~)~~).

*Al-Kouatly, et al 2022*

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

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

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

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# Prenatal Diagnosis ~~Via~~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~~)~~).

*Zhou J, et al. 2021*

An article by Zhou, et al prospectively evaluated the clinical utility of whole genome sequencing (WGS) compared with standard chromosome microarray (CMA) in fetuses with structural anomalies. WGS was found to have a diagnostic rate of 19.8%, and was able to provide additional clinical information, such as a balanced translocation. "

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

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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 (#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).

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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).

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## Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies

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

This cohort study of ultrasound findings of 424 fetuses in the Netherlands concluded with the recommendation for "testing of fetuses with solely an increased NT after chromosomal abnormalities have been excluded when the NT is greater than or equal to 5.0 mm. We also recommend testing when the NT is greater than or equal to 3.5 mm and at least one of the following anomalies is present: distended jugular lymph sacs (JLS), hydrops fetalis, polyhydramnios, pleural effusion and cardiac defects." (p. 660)

"In general, an NGS panel of known rasopathy genes should be used when a rasopathy is suspected. Although we did not find pathogenic variants in every gene in the panel, in all genes, a prenatal phenotype has been documented in literature. Therefore, a smaller panel is not advisable. However, in countries where an extensive panel is not available, testing for only *PTPN11* gene would catch 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.

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## Prenatal Diagnosis for Skeletal Dysplasias

*Krakow et al 2009*

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

*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).

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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.

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

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| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
|---|---|---|---|
| Converted corporate policy to local policy | 09/23 | 11/27/23 | |

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
|---|---|---|---|
| Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Policy Reference Table: removed "Chromosomal FISH (Aneuploidy) Analysis and related content; removed "Exome or Genome Sequencing for Pregnancy Loss" and related content; under Prenatal Diagnosis for Single-Gene Disorders: added "0218U"; added 81178-81189; added "81243"; added 81251-81259; removed "81271, 81274"; added "81285"; added "81329"; added "81231"; added "81336"; added "81362, 81363"; added 81401-81407. For Other Related Policies: added "and Molecular". For Criteria; removed "FISH (Aneuploidy) Analysis…"; for Chromosomal Microarray Analysis (CMA) for Pregnancy Loss: I.A.1. removed "pregnancy loss at 20 weeks of gestation…"; added "history of recurrent pregnancy loss"; I.A.2. replaced "after" with "at or greater than"; for Conventional Karotype Analysis for Pregnancy Loss: I.A. removed "miscarriage (defined as having…"; added "pregnancy loss"; removed Exome or Genome Sequencing for Pregnancy Loss and related content; for Prenatal Diagnosis for Single Gene Disorders: for II.-IV added "Prenatal diagnosis for single gene disorders…"; added "0218U"; added 81178-81189; added "81243"; added 81251-81259; removed "81271, 81274"; added "81285"; added "81329"; added "81231"; added "81336"; added "81362, 81363"; added 81401-81407; I.A.4. replaced "previous affected" with "history of a previous"; removed "germline mosaicism"; added "the member/enrollee"; added "to have germline mosaicism"; removed I.D. "The test has been ordered…"; for Prenatal Diagnosis for Noonan Spectrum Disorders/Rasopathies: removed I.D-I.E.; for Prenatal Diagnosis for Skeletal Displasias: removed I.A.7. "AND The member/enrollee's current pregnancy…"; removed I.B. "IBPPL1…"; removed I.C. "The panel has been ordered…"; for Prenatal Diagnosis via Exome Sequencing: removed I.D.-I.E.; added II. "Prenatal diagnosis, via smniocentesis…"; added III. "Exome of genome sequencing…". For Background and Rationale; Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis: removed "(10). If a structural…"; for Chromosomal Microarray Analysis (CMA) for Pregnancy Loss: removed "Because of the advantages…"; added "The ACOG and SMFM…"; added "(ASRM)"; for Conventional Karotype Analysis for Pregnancy Loss: removed "occurring "after two consecutive…""; removed "Exome or Genone Sequencing for Pregnancy Loss…"; added "a distinct disorder…"; for Prenatal Diagnosis for Single-Gene Disorders: added "Some autosomal dominant…"; added "American College of Obstetricians and Gynecologists…"; added "ACOG released a committee…"; for Prenatal Diagnosis for Skeletal Dysplasias: removed "The following fetal ultrasound…"; added "In addition, close attention…"; added "Scocchia, et al…"; for Prenatal Diagnosis via Exome Sequencing: removed "Both pretest counseling"; for Prenatal Diagnosis via Whole Genome Sequencing: removed "Yang Z, Sun J". | 12/23 | 2/27/24 | |

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
|---|---|---|---|
| Semi-annual review. Updated title to reflect V2.2024 version. In Prenatal Diagnosis for Noonan Spectrum Disorders/, minor expansion in coverage: changed nuchal translucency requirement to 3.0 mm to better align with ACOG guidelines and published literature. In Prenatal Diagnosis for Noonan Spectrum Disorders/ RASopathies, removed minimum gene list; at present there is limited rationale for inclusion. In Definitions, clarified that the definition of "major malformations" includes fetal growth restriction/IUGR, as primary literature suggests that fetuses with IUGR have a relatively high diagnostic yield via exome sequencing. In Chromosomal Microarray Analysis (CMA) for Pregnancy Loss, updated requirements for counseling to be consistent with coverage criteria throughout this policy. In Prenatal Diagnosis via Exome Sequencing, removed one criterion from this section regarding exome or genome sequencing for pregnancy loss on products of conception, based on lack of volume in claims. Minor rewording for clarity throughout. Coding, reference-table, background and references updated. | 06/24 | 9/17/24 | 10/17/24 |
| Semi-annual review. Updated title to reflect V1.2025 version. Prenatal Diagnosis via Genome Sequencing: Reformatted Policy Reference Table and Background and Rationale. Prenatal Diagnosis for Skeletal Dysplasias: Streamlined portions of Background and Rationale section for brevity. Prenatal Diagnosis for Single Gene Disorders: Criteria moved to the General policy (no changes to criteria itself). Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis: Added PLA code 0496U to criteria set to match policy reference table; Added new PLA test to Policy Reference Table. Prenatal Diagnosis via Exome Sequencing: Removed out of date reference and added new one (Background and Rationale and References). | 1/25 | 3/31/25 | 5/1/25 |
| Annual review. Policy title changed from Concert Genetic Testing Prenatal Diagnosis (via Amniocentesis, CVS, or PUBS) and Pregnancy Loss to Concert Genetic Testing: Prenatal Diagnosis. Prenatal Diagnosis via Genome Sequencing criteria: noted that current evidence does not support for "all other indications." "Investigational" policy statements changed to note that "current evidence does not support…" Coding table, rationale and references updated. | 03/26 | | |

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**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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