BSC_CON_2.06	Genetic Testing: Prenatal Diagnosis (Via Amniocentesis, CVS, or PUBS) And Pregnancy Loss		
Original Policy Date:	February 1, 2023	**Effective Date:**	September 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 25

Example Test Table

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

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes
Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis	Reveal SNP Microarray - Prenatal (Integrated Genetics)	81228, 81229, 81265, 88235
	Prenatal Whole Genome Chromosomal Microarray (GeneDx)	
Conventional Karyotype Analysis for Prenatal Diagnosis	Chromosome Analysis, Amniotic Fluid (GeneDx)	88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291
	Chromosome Analysis, Chorionic Villus Sample (Quest Diagnostics)	
	Chromosome Analysis, Amniotic Fluid (Quest Diagnostics)	
Chromosomal Microarray Analysis (CMA) for Pregnancy Loss	SNP Microarray-Products of Conception (POC)/Tissue (Reveal) (Labcorp)	81228, 81229, 81265, 88235
	Chromosomal Microarray, POC, ClariSure Oligo-SNP (Quest Diagnostics)	
Conventional Karyotype Analysis for Pregnancy Loss	Chromosome Analysis, POC, Tissue (Bioreference Labs)	88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291
	Chromosome Analysis, Products of Conception (POC) (GeneDx)	
Prenatal Diagnosis for Single-Gene Disorders	Various Targeted Mutation Analysis	0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81329, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402,

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes
		81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265
Prenatal Diagnosis for Noonan Spectrum Disorders/RASopathies	Prenatal Noonan Spectrum Disorders Panel (GeneDx)	81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235
	Prenatal Noonan Syndrome (Integrated Genetics)	
Prenatal Diagnosis for Skeletal Dysplasias	Prenatal Skeletal Dysplasia Panel (GeneDx)	81404, 81405, 81408, 81479, 81265, 88235
	Skeletal Dysplasia Core NGS Panel (Connective Tissue Gene Tests)	
Prenatal Diagnosis via Exome Sequencing	XomeDx Prenatal-Comprehensive (GeneDx)	81415, 81416, 81265, 88235
	Prenatal Exome Sequencing (Greenwood Genetic Center)	
Prenatal Diagnosis via Genome Sequencing	Prenatal Whole Genome Sequencing	81425, 81426, 81427, 88235, 81265, 0335U, 0336U

Policy Statement

Chromosomal Microarray Analysis (CMA) For Prenatal Diagnosis

I. Chromosome microarray analysis (81228, 81229, 81265, 88235) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when:
   A. The member has received counseling regarding the benefits and limitations of prenatal screening and diagnostic testing (including chromosome microarray via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities.

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

Conventional Karyotype Analysis For Prenatal Diagnosis

III. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when:
   A. The member has received counseling regarding the benefits and limitations of prenatal screening and diagnostic testing (including karyotyping via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities.

IV. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications.

Chromosomal Microarray Analysis (CMA) For Pregnancy Loss

V. Chromosomal microarray analysis (81228, 81229, 81265, 88235) on products of conception (POC) may be considered **medically necessary** as an alternative to conventional karyotype analysis when **both** of the following criteria are met:
   A. The member meets **one** of the following:
      1. The member has a history of recurrent pregnancy loss

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

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

VI. Chromosome microarray analysis (81228, 81229, 81265, 88235) on products of conception (POC) is considered **investigational** for all other indications.

Conventional Karyotype Analysis For Pregnancy Loss

VII. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) on products of conception (POC) may be considered **medically necessary** when:
   A. The member has a history of recurrent pregnancy loss.

VIII. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) on products of conception (POC) is considered **investigational** for all other indications.

Prenatal Diagnosis For Single Gene Disorders

IX. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, may be considered **medically necessary** when **all** of the following criteria are met:
   A. The member meets **any** of the following:
      1. At least one biological parent has a known pathogenic variant for an autosomal dominant condition
      2. Both biological parents are known carriers of an autosomal recessive condition
      3. One biological parent is suspected or known to be a carrier of an X-linked condition
      4. The member has a history of a previous child with a genetic condition and the member is suspected to have germline mosaicism
   B. The natural history of the disease is well-understood, and there is a high likelihood that the disease has high morbidity
   C. The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood

X. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, for adult onset single-gene disorders (examples: hereditary cancer syndromes such as *BRCA1/2,* etc.) is considered **not medically necessary**.

XI. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209,

81221, 81239, 81242. 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for variants of unknown significance (VUS).

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

Prenatal Diagnosis For Noonan Spectrum Disorders/Rasopathies

XIII. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235) may be considered **medically necessary** when **all** of the following criteria are met:
- A. The member's current pregnancy has had a normal karyotype and/or microarray
- 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
  2. The member's current pregnancy has **both** of the following:
     a. An increased nuchal translucency of at least 3.5mm
     b. **One** of the following ultrasound findings:
        i. Distended jugular lymph sacs (JLS)
        ii. Hydrops fetalis
        iii. Polyhydramnios
        iv. Pleural effusion
        v. Cardiac defects (e.g., pulmonary valve stenosis, atrioventricular septal defect, coarctation of the aorta, hypertrophic cardiomyopathy, atrial septal defect, etc.)
- C. The panel being ordered includes, at a minimum, the following genes: *PTPN11, RAF1, RIT1, SOS1*

XIV. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235) is considered **investigational** for all other indications.

Prenatal Diagnosis For Skeletal Dysplasias

XV. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265, 88235) may be considered **medically necessary** when **both** of the following criteria are met:
- A. The member's current pregnancy has **any** of the following ultrasound findings:
  1. Long bones less than 5th percentile
  2. Poor mineralization of the calvarium
  3. Fractures of long bones (particularly femora)
  4. Bent/bowed bones
  5. Poor mineralization of the vertebrae
  6. Absent/hypoplastic scapula
  7. Equinovarus

B. The panel being ordered includes, at a minimum, the following genes: *COL1A1*, *COL1A2*, *COL2A1*, *FGFR3*

XVI. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265, 88235) is considered **investigational** for all other indications.

Prenatal Diagnosis Via Exome Sequencing

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

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

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

Prenatal Diagnosis Via Genome Sequencing

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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.

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 Rationale for more information).

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

Coding
See the Codes table for details.

Description

Prenatal diagnostic testing may be used to identify genetic conditions in fetuses at an increased risk based on prenatal screening or for women who choose to undergo diagnostic testing due to other risk factors, such as abnormal ultrasound findings, previous pregnancy with aneuploidy, etc. Prenatal diagnostic testing for genetic disorders is performed on fetal cells derived from amniotic fluid, and/or percutaneous umbilical blood sampling (PUBS) (cordocentesis) or from placental cells via chorionic villus sampling (CVS). Genetic testing techniques include conventional chromosome analysis, chromosome fluorescence in situ hybridization (FISH), chromosomal microarray analysis (CMA), targeted or Sanger sequencing, and next-generation sequencing (NGS).

Genetic testing may also be used in an attempt to determine the cause of isolated or recurrent pregnancy loss, including miscarriages, intrauterine fetal demise (IUFD), and stillbirth. The evaluation of both recurrent and isolated miscarriages and IUFD or stillbirth may involve genetic testing of the products of conception (POC) and/or testing of fetal/placental cells from amniotic fluid, CVS, or PUBS if available. Such testing of POC has typically been carried out through cell culture and karyotyping of cells in metaphase. However, the analysis of fetal or placental tissue has been inhibited by the following limitations: the need for fresh tissue, the potential for cell culture failure, and the potential for maternal cell contamination. Potential benefits of identifying a genetic abnormality in a miscarriage or IUFD include reducing emotional distress for families, eliminating the need for additional testing to assess for causes of pregnancy loss, and assisting in reproductive decision making for future pregnancies.

The decision to elect a prenatal diagnostic test and/or genetic testing following pregnancy loss should be made jointly by the mother and/or parents and the treating clinician. Genetic counseling, including facilitation of decision making, is strongly recommended.

In most cases, prenatal genetic testing for single gene disorders using molecular genetic testing requires knowledge of the familial genetic variant which has been identified in a family member (e.g., biological mother, biological father, and/or sibling).

Related Policies

This policy document provides coverage criteria for prenatal or pregnancy loss diagnostic testing, and does not address the use of conventional chromosome analysis, CMA, or FISH for preimplantation genetic testing or the evaluation of suspected chromosome abnormalities in the postnatal period. Please refer to:

- ***Genetic Testing: Noninvasive Prenatal Screening (NIPS)*** for coverage criteria related to prenatal cell-free DNA screening tests.

- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to carrier screening for genetic disorders.
- ***Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability and Developmental Delay*** for coverage criteria related to suspected chromosome abnormalities in the postnatal period.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to prenatal diagnostic or pregnancy loss genetic testing that is not specifically discussed in this or other non-general policies

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

- N/A

Rationale

Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis
American College of Obstetricians and Gynecologists (ACOG)
An ACOG practice bulletin (#162, 2016) states the following:

- Chromosomal aberrations that are smaller than the resolution of conventional karyotype also can result in phenotypic anomalies; these copy number variants can be detected in the fetus using chromosomal microarray analysis. When structural abnormalities are detected by prenatal ultrasound examination, chromosomal microarray will identify clinically significant chromosomal abnormalities in approximately 6% of the fetuses that have a normal karyotype. 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 (11), and it is recommended that chromosomal microarray analysis be made available to any patient choosing to undergo invasive diagnostic testing. (p. e.110)

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)

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, 2020) supports the following evaluation for pregnancy loss in their 2016 (reaffirmed 2020) statement:
"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)

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)

Prenatal Diagnosis for Single-Gene Disorders
National Society of Genetic Counselors (NSGC)
The National Society of Genetic Counselors updated a position statement (2019) regarding prenatal testing for adult-onset conditions, stating the following:
"The National Society of Genetic Counselors (NSGC) does not recommend prenatal genetic testing for known adult-onset conditions if pregnancy or childhood management will not be affected. Due to potential medical and ethical complexities, NSGC recommends that prior to undergoing testing, prospective parents meet with a genetic counselor or other healthcare specialists with genetics expertise to discuss the implications of prenatal testing for adult-onset conditions. Pre-test counseling should include a discussion of the natural history of the condition, availability of treatments or interventions, concerns that prenatal testing for adult-onset conditions may deny a child's future autonomy, and potential for genetic discrimination."

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

All pregnant women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors. Patients with an increased risk of a fetal genetic disorder include those in the following categories:

- Older maternal age
- Older paternal age
- Prior child with structural birth defect
- Previous fetus or child with autosomal trisomy or sex chromosome aneuploidy
- Structural anomalies identified by ultrasonography
- Parental carrier of chromosome rearrangement
- Parental aneuploidy or aneuploidy mosaicism
- Parental carrier of a genetic disorder
- Biological parent who is affected by an autosomal dominant disorder. (p. e112-e113)

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

American College of Obstetricians and Gynecologists (ACOG)
ACOG released a committee opinion (no. 693) in April 2017 regarding counseling about genetic testing and communication of genetic test results.

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

A discussion of the sensitivity and specificity of the test for each of the disorders being tested is important to ensure patient understanding. For example, in the case of expanded carrier screening, patients should be informed of the overall range of the carrier detection rate and the range of residual risk of the disorders examined. With reference to each patient's specific a priori risk, the patient should be informed of the meaning and significance of positive, negative, or indeterminate test results, as well as results that are normal but may have variable phenotypes. This discussion of the positive predictive value and negative predictive value of the test result facilitates a discussion of the potential need for follow-up diagnostic testing. (p. 3)

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)

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. If the patient cannot travel, arrangements may be able to be made for evaluation of ultrasound videotapes or hard copy images. (p. 5)
- Fetuses with long bone parameters greater than 3 SD below the mean should be strongly suspected of having a skeletal dysplasia, especially if the head circumference is greater than the 75th centile. (p. 5)
- Lethality should be determined by chest circumference to abdominal circumference ratio and/or femur length to abdominal circumference measurement ratio. A chest-to abdominal circumference ratio of <0.6 or femur length to abdominal circumference ratio of 0.16 strongly suggests a perinatal lethal disorder, although there are exceptions. The findings should be conveyed to the physicians caring for the patient and to the patient. (p. 5)
- In addition, close attention should be paid to the shape and mineralization pattern of the fetal calvarium and fetal skeleton (poor or ectopic mineralization). Determining the elements of the skeleton that are abnormal, coupled with the findings of mineralization and shape of the bones can aid in diagnosis. (p. 3)

The guidelines also state:

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

Scocchia, et al.
A 2021 study of the clinical utility of multigene panel testing for an unselected population of individuals with suspected skeletal dysplasia demonstrated a high diagnostic yield in prenatal cases. (p. 1)

A molecular diagnosis was established in 42% of patients (228/543). Diagnostic variants were identified in 71 genes, with variation in nearly half of these genes contributing to a molecular diagnosis for a single patient in this cohort. Overall, the most common genes in which molecular diagnoses were identified included: *COL2A1* associated with type II collagenopathies; *FGFR3* associated with achondroplasia, thanatophoric dysplasia, hypochondroplasia, and other conditions such as FGFR-related craniosynostoses; and *COL1A1* or *COL1A2*, associated with osteogenesis imperfecta. Together, these four genes accounted for over one third of all molecular diagnoses across the cohort. (p. 2-3)

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)

Sparks et al 2020
A large case series published in the New England Journal of Medicine evaluated 127 cases of unexplained nonimmune hydrops fetalis (NIHF) via exome sequencing. (p. 1746) Non-diagnostic karyotype or chromosome microarray was a requirement for eligibility in the study. (p. 1747) Diagnostic genetic variants were found in 29% of cases. (p. 1746) Therefore, the authors conclude with the following: "These data support the use of exome sequencing for NIHF cases with non-diagnostic results of chromosomal microarray analysis or karyotype analysis in order to inform prognosis, establish recurrence risk, and direct prenatal and postnatal clinical care." (p. 1755)

Prenatal Diagnosis Via Whole Genome Sequencing

American College of Obstetricians and Gynecologists (ACOG) and Society for Maternal Fetal Medicine (SMFM)
ACOG and SMFM (2016, reaffirmed in 2020) issued a committee opinion No. 682 which included the following conclusions and recommendations for the use of chromosomal microarray testing and next-generation sequencing in prenatal diagnosis. Note that while whole exome sequencing is addressed in this opinion, whole genome sequencing is not yet recommended:

"Whole-exome sequencing also is a broad molecular diagnostic approach to identify the etiology for fetal abnormalities, and whole-exome sequencing of fetal DNA obtained by amniocentesis, chorionic villi, or umbilical cord blood is being offered on a research basis in some laboratories and for specific clinical indications in other laboratories. Published data on the prenatal applications of whole-exome sequencing are limited to case series and case reports. However, these series suggest that a genomic abnormality may be identified in up to 20–30% of fetuses with multiple anomalies for which standard genetic testing results (i.e., karyotype, microarray, or both) are normal. These cases illustrate

how whole-exome sequencing potentially may be used to provide families with a definitive diagnosis, accurate estimates of recurrence risk, and even the options of preimplantation genetic testing or early prenatal diagnosis in a future pregnancy."

Zhou J, et al. 2021
"Whole exome sequencing (WES), which detects SNVs, INDELs, and CNVs covering multiple exons, has been proven to be a powerful tool in prenatal diagnosis. In clinical practice, WES can be conducted in CMA-negative cases to further search for single-base lesions. Emerging studies have shown that WES has a detection rate of 8.5% to 10% in fetal structural abnormalities with normal karyotype and CMA results. CMA followed by WES considerably increases the diagnostic yield, and is increasingly accepted as a routine test strategy in clinical practice; however, given the time-sensitive nature of the prenatal stage and the potential inaccessibility of adequate fetal samples, sequential testing is time-consuming and requires a large amount of DNA as input. More importantly, it is unable to detect certain types of variation, such as balanced translocation or noncoding SNVs/INDELs. Whole genome sequencing (WGS) has the potential to detect almost all types of genomic variants with a low input-DNA requirement (approx. 100 ng) and is proposed to be beneficial in prenatal diagnosis." (p. 1)

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

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. Reaffirmed 2020. 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. 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
5. 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
6. 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
7. "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.
8. 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

9. 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;136(4):e48-e69. doi:10.1097/AOG.0000000000004084
10. Roberts AE. Noonan Syndrome. 2001 Nov 15 [Updated 2022 Feb 17]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1124/
11. 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.
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/10.3390/genes12030376
13. 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* 16, 412 (2021). https://doi.org/10.1186/s13023-021-02025-7
14. Committee Opinion No. 693: Counseling About Genetic Testing and Communication of Genetic Test Results. *Obstet Gynecol*. 2017;129(4):e96-e101. doi:10.1097/AOG.0000000000002020

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0218U	Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants
	0335U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants
	0336U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., parent)
	0469U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination ***(Code effective 7/1/2024)***
	81174	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
	81177	ATN1 (atrophin 1) (e.g., dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81178	ATXN1 (ataxin 1) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81179	ATXN2 (ataxin 2) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81180	ATXN3 (ataxin 3) (e.g., spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81181	ATXN7 (ataxin 7) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81182	ATXN8OS (ATXN8 opposite strand [non-protein coding]) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81183	ATXN10 (ataxin 10) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; full gene sequence

Type	Code	Description
	81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; known familial variant
	81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (e.g., myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81188	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81189	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; full gene sequence
	81190	CSTB (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; known familial variant(s)
	81200	ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)
	81202	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81204	AR (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (e.g., expanded size or methylation status)
	81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (e.g., maple syrup urine disease) gene analysis, common variants (e.g., R183P, G278S, E422X)
	81209	BLM (Bloom syndrome, RecQ helicase-like) (e.g., Bloom syndrome) gene analysis, 2281del6ins7 variant
	81221	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants
	81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
	81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
	81239	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; characterization of alleles (e.g., expanded size)
	81242	FANCC (Fanconi anemia, complementation group C) (e.g., Fanconi anemia, type C) gene analysis, common variant (e.g., IVS4+4A>T)
	81243	FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81244	FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and promoter methylation status)
	81248	DMPK (DM1 protein kinase) (e.g., myotonic dystrophy type 1) gene analysis; characterization of alleles (e.g., expanded size)
	81250	G6PC (glucose-6-phosphatase, catalytic subunit) (e.g., Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (e.g., R83C, Q347X)
	81251	GBA (glucosidase, beta, acid) (e.g., Gaucher disease) gene analysis, common variants (e.g., N370S, 84GG, L444P, IVS2+1G>A)
	81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; known familial variants

Type	Code	Description
	81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., nonsyndromic hearing loss) gene analysis, common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
	81255	HEXA (hexosaminidase A [alpha polypeptide]) (e.g., Tay-Sachs disease) gene analysis, common variants (e.g., 1278insTATC, 1421+1G>C, G269S)
	81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; common deletions or variant (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, Constant Spring)
	81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
	81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
	81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (e.g., familial dysautonomia) gene analysis, common variants (e.g., 2507+6T>C, R696P)
	81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (e.g., pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [e.g., buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
	81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
	81284	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
	81285	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; characterization of alleles (e.g., expanded size)
	81286	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; full gene sequence
	81289	FXN (frataxin) (e.g., Friedreich ataxia) gene analysis; known familial variant(s)
	81290	MCOLN1 (mucolipin 1) (e.g., Mucolipidosis, type IV) gene analysis, common variants (e.g., IVS3-2A>G, del6.4kb)
	81303	MECP2 (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; known familial variant
	81312	PABPN1 (poly[A] binding protein nuclear 1) (e.g., oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81329	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; dosage/deletion analysis (e.g., carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
	81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330)
	81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome), methylation analysis

Type	Code	Description
	81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g., *S and *Z)
	81336	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; full gene sequence
	81337	SMN1 (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy) gene analysis; known familial sequence variant(s)
	81343	PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81344	TBP (TATA box binding protein) (e.g., spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (e.g., expanded) alleles
	81361	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (e.g., HbS, HbC, HbE)
	81362	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
	81363	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
	81364	HBB (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
	81400	Molecular Pathology Procedure Level 1
	81401	Molecular Pathology Procedure Level 2
	81402	Molecular Pathology Procedure Level 3
	81403	Molecular Pathology Procedure Level 4
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
	81406	Molecular Pathology Procedure Level 7
	81407	Molecular Pathology Procedure Level 8
	81408	Molecular Pathology Procedure Level 9
	81415	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
	81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81426	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
	81427	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
	81442	Noonan spectrum disorders (e.g., Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
	81479	Unlisted molecular pathology procedure
	88235	Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells

Type	Code	Description
	88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
	88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
	88263	Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding
	88264	Chromosome analysis; analyze 20-25 cells
	88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
	88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding
	88280	Chromosome analysis; additional karyotypes, each study
	88291	Cytogenetics and molecular cytogenetics, interpretation and report
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2023	New policy.
02/01/2024	Annual review. Policy statement, guidelines and literature updated.
09/01/2024	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an

authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Genetic Testing: Prenatal Diagnosis (Via Amniocentesis, CVS, or PUBS) and Pregnancy Loss BSC_CON_2.06 **Policy Statement:** **Chromosomal Microarray Analysis (CMA) For Prenatal Diagnosis** I. Chromosome microarray analysis (81228, 81229, 81265, 88235) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when: A. The member has received counseling regarding the benefits and limitations of prenatal screening and diagnostic testing (including chromosome microarray via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities. II. Chromosome microarray analysis (81228, 81229, 81265, 88235) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications. **Conventional Karyotype Analysis For Prenatal Diagnosis** III. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when: A. The member has received counseling regarding the benefits and limitations of prenatal screening and diagnostic testing (including karyotyping via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities. IV. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications. **Chromosomal Microarray Analysis (CMA) For Pregnancy Loss**	**Genetic Testing: Prenatal Diagnosis (Via Amniocentesis, CVS, or PUBS) And Pregnancy Loss BSC_CON_2.06** **Policy Statement:** **Chromosomal Microarray Analysis (CMA) For Prenatal Diagnosis** I. Chromosome microarray analysis (81228, 81229, 81265, 88235) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when: A. The member has received counseling regarding the benefits and limitations of prenatal screening and diagnostic testing (including chromosome microarray via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities. II. Chromosome microarray analysis (81228, 81229, 81265, 88235) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications. **Conventional Karyotype Analysis For Prenatal Diagnosis** III. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when: A. The member has received counseling regarding the benefits and limitations of prenatal screening and diagnostic testing (including karyotyping via amniocentesis, CVS or PUBS) for fetal chromosome abnormalities. IV. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications. **Chromosomal Microarray Analysis (CMA) For Pregnancy Loss**

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V. Chromosomal microarray analysis (81228, 81229, 81265, 88235) on products of conception (POC) may be considered **medically necessary** as an alternative to conventional karyotype analysis when **both** of the following criteria are met: A. The member meets **one** of the following: 1. The member has a history of recurrent pregnancy loss 2. The member has a pregnancy loss at or greater than 20 weeks of gestation (i.e., IUFD or stillbirth) 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	V. Chromosomal microarray analysis (81228, 81229, 81265, 88235) on products of conception (POC) may be considered **medically necessary** as an alternative to conventional karyotype analysis when **both** of the following criteria are met: A. The member meets **one** of the following: 1. The member has a history of recurrent pregnancy loss 2. The member has a pregnancy loss at or greater than 20 weeks of gestation (i.e., IUFD or stillbirth) 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
VI. Chromosome microarray analysis (81228, 81229, 81265, 88235) on products of conception (POC) is considered **investigational** for all other indications.	VI. Chromosome microarray analysis (81228, 81229, 81265, 88235) on products of conception (POC) is considered **investigational** for all other indications.
Conventional Karyotype Analysis For Pregnancy Loss VII. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) on products of conception (POC) may be considered **medically necessary** when: A. The member has a history of recurrent pregnancy loss.	**Conventional Karyotype Analysis For Pregnancy Loss** VII. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) on products of conception (POC) may be considered **medically necessary** when: A. The member has a history of recurrent pregnancy loss.
VIII. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) on products of conception (POC) is considered **investigational** for all other indications.	VIII. Conventional karyotype analysis (88235, 88261, 88262, 88263, 88264, 88267, 88269, 88280, 88291) on products of conception (POC) is considered **investigational** for all other indications.
Prenatal Diagnosis For Single Gene Disorders IX. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255,	**Prenatal Diagnosis For Single Gene Disorders** IX. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255,

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81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, may be considered **medically necessary** when **all** of the following criteria are met: A. The member meets **any** of the following: 1. At least one biological parent has a known pathogenic variant for an autosomal dominant condition 2. Both biological parents are known carriers of an autosomal recessive condition 3. One biological parent is suspected or known to be a carrier of an X-linked condition 4. The member has a history of a previous child with a genetic condition and the member is suspected to have germline mosaicism B. The natural history of the disease is well-understood, and there is a high likelihood that the disease has high morbidity C. The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood	81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, may be considered **medically necessary** when **all** of the following criteria are met: A. The member meets **any** of the following: 1. At least one biological parent has a known pathogenic variant for an autosomal dominant condition 2. Both biological parents are known carriers of an autosomal recessive condition 3. One biological parent is suspected or known to be a carrier of an X-linked condition 4. The member has a history of a previous child with a genetic condition and the member is suspected to have germline mosaicism B. The natural history of the disease is well-understood, and there is a high likelihood that the disease has high morbidity C. The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood
X. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, for adult onset single-gene disorders (examples: hereditary cancer syndromes such as *BRCA1/2,* etc.) is considered **not medically necessary**.	X. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, for adult onset single-gene disorders (examples: hereditary cancer syndromes such as *BRCA1/2,* etc.) is considered **not medically necessary**.
XI. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242. 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255,	XI. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242. 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255,

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BEFORE	**AFTER**
81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for variants of unknown significance (VUS).	81257, 81258, 81259, 81260, 81269, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for variants of unknown significance (VUS).
XII. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284-81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for all other indications.	XII. Prenatal diagnosis for single-gene disorders (0218U, 81174, 81177, 81178, 81179, 81180, 81181, 81182, 81183, 81184, 81185, 81186, 81187, 81188, 81189, 81190, 81200, 81202, 81204, 81205, 81209, 81221, 81239, 81242, 81243, 81244, 81248, 81250, 81251, 81252, 81253, 81254, 81255, 81257, 81258, 81259, 81260, 81269, 81284-81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81336, 81337, 81343, 81344, 81361, 81362, 81263, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS, is considered **investigational** for all other indications.
Prenatal Diagnosis For Noonan Spectrum Disorders/Rasopathies	**Prenatal Diagnosis For Noonan Spectrum Disorders/Rasopathies**
XIII. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235) may be considered **medically necessary** when **all** of the following criteria are met: A. The member's current pregnancy has had a normal karyotype and/or microarray 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 2. The member's current pregnancy has **both** of the following: a. An increased nuchal translucency of at least 3.5mm b. **One** of the following ultrasound findings: i. Distended jugular lymph sacs (JLS) ii. Hydrops fetalis iii. Polyhydramnios iv. Pleural effusion	XIII. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235) may be considered **medically necessary** when **all** of the following criteria are met: A. The member's current pregnancy has had a normal karyotype and/or microarray 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 2. The member's current pregnancy has **both** of the following: a. An increased nuchal translucency of at least 3.5mm b. **One** of the following ultrasound findings: i. Distended jugular lymph sacs (JLS) ii. Hydrops fetalis iii. Polyhydramnios iv. Pleural effusion

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v. Cardiac defects (e.g., pulmonary valve stenosis, atrioventricular septal defect, coarctation of the aorta, hypertrophic cardiomyopathy, atrial septal defect, etc.) C. The panel being ordered includes, at a minimum, the following genes: *PTPN11, RAF1, RIT1, SOS1*	v. Cardiac defects (e.g., pulmonary valve stenosis, atrioventricular septal defect, coarctation of the aorta, hypertrophic cardiomyopathy, atrial septal defect, etc.) C. The panel being ordered includes, at a minimum, the following genes: *PTPN11, RAF1, RIT1, SOS1*
XIV. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235) is considered **investigational** for all other indications.	XIV. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81407, 81479, 81442, 81265, 88235) is considered **investigational** for all other indications.
Prenatal Diagnosis For Skeletal Dysplasias XV. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265, 88235) may be considered **medically necessary** when **both** of the following criteria are met: A. The member's current pregnancy has **any** of the following ultrasound findings: 1. Long bones less than 5th percentile 2. Poor mineralization of the calvarium 3. Fractures of long bones (particularly femora) 4. Bent/bowed bones 5. Poor mineralization of the vertebrae 6. Absent/hypoplastic scapula 7. Equinovarus B. The panel being ordered includes, at a minimum, the following genes: *COL1A1*, *COL1A2*, *COL2A1*, *FGFR3*	**Prenatal Diagnosis For Skeletal Dysplasias** XV. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265, 88235) may be considered **medically necessary** when **both** of the following criteria are met: A. The member's current pregnancy has **any** of the following ultrasound findings: 1. Long bones less than 5th percentile 2. Poor mineralization of the calvarium 3. Fractures of long bones (particularly femora) 4. Bent/bowed bones 5. Poor mineralization of the vertebrae 6. Absent/hypoplastic scapula 7. Equinovarus B. The panel being ordered includes, at a minimum, the following genes: *COL1A1*, *COL1A2*, *COL2A1*, *FGFR3*
XVI. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265, 88235) is considered **investigational** for all other indications.	XVI. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479, 81265, 88235) is considered **investigational** for all other indications.
Prenatal Diagnosis Via Exome Sequencing	**Prenatal Diagnosis Via Exome Sequencing**

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XVII. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265, 88235) may be considered **medically necessary** when **all** of the following criteria are met: A. The member's current pregnancy has **either** of the following: 1. Non-immune hydrops fetalis 2. Two or more major malformations on ultrasound, which are affecting different organ systems B. The member's current pregnancy has had a karyotype and/or microarray performed and the results were negative/normal C. Alternate etiologies have been considered and ruled out when possible (examples: environmental exposure, injury, infection, maternal condition)	XVII. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265, 88235) may be considered **medically necessary** when **all** of the following criteria are met: A. The member's current pregnancy has **either** of the following: 1. Non-immune hydrops fetalis 2. Two or more major malformations on ultrasound, which are affecting different organ systems B. The member's current pregnancy has had a karyotype and/or microarray performed and the results were negative/normal C. Alternate etiologies have been considered and ruled out when possible (examples: environmental exposure, injury, infection, maternal condition)
XVIII. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265, 88235) is considered **investigational** for all other indications.	XVIII. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265, 88235) is considered **investigational** for all other indications.
XIX. Exome or genome sequencing (81265, 81415, 81416, 88235) for pregnancy loss on products of conception (POC) is considered **investigational**.	**XIX.** Exome or genome sequencing (81265, 81415, 81416, 88235) for pregnancy loss on products of conception (POC) is considered **investigational**.
Prenatal Diagnosis Via Genome Sequencing XX. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using genome sequencing (81425, 81426, 81427, 88235, 81265, 0335U, 0336U) is considered **investigational**.	**Prenatal Diagnosis Via Genome Sequencing** XX. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using genome sequencing (81425, 81426, 81427, 88235, 81265, 0335U, 0336U) is considered **investigational**.