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

Example Test Table

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Chromosome FISH (Aneuploidy) Panel	Aneuploidy Panel by FISH (ARUP Laboratories)	88271, 88275
Chromosomal Microarray Analysis for Prenatal Diagnosis	Reveal® SNP Microarray - Prenatal (Integrated Genetics)	81229
	Prenatal Whole Genome Chromosomal Microarray (GeneDx)	
Conventional Chromosome Analysis for Prenatal Diagnosis	Chromosome Analysis, Amniotic Fluid (GeneDx)	88235, 88280, 88291
	Chromosome Analysis, Chorionic Villus Sample (Quest Diagnostics)	88235, 88267, 88280
	Chromosome Analysis, Amniotic Fluid (Quest Diagnostics)	88235, 88269, 88280
Chromosomal Microarray Analysis for Pregnancy Loss	SNP Microarray-Products of Conception (POC)/Tissue (Reveal) (LabCorp)	81229
	Chromosomal Micorarray, POC, ClariSure Oligo-SNP (Quest Diagnostics)	
Exome or Genome Sequencing for Pregnancy Loss	PGxome Prenatal Exome Test (PreventionGenetics)	81415, 81416, 81417, 81425, 81426, 81427, 81265
Prenatal Diagnosis for Single-Gene Disorders	Various Targeted Mutation Analysis	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, 81256, 81257, 81258, 81259, 81260, 81269, 81271, 81274, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265
	Prenatal Noonan Spectrum Disorders Panel (GeneDx)	81404, 81405, 81406

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Prenatal Diagnosis for Noonan Spectrum Disorders/Rasopathies	Prenatal Noonan Syndrome (LabCorp)	81442
Prenatal Diagnosis for Skeletal Dysplasias	Prenatal Skeletal Dysplasia Panel (GeneDx)	81404, 81405, 81408
	Skeletal Dysplasia Core NGS Panel (Connective Tissue Gene Tests)	81408, 81479
Prenatal Diagnosis via Exome Sequencing	XomeDx Prenatal-Comprehensive (GeneDx)	81415, 81416, 81417, 81265
	Prenatal Exome Sequencing (Greenwood Genetic Center)	81415, 81416, 81417, 81265
Prenatal Diagnosis via Whole Genome Sequencing	Prenatal Whole Genome Sequencing	81425, 81426, 81427, 88235, 81265, 0335U, 0336U

Policy Statement

Chromosomal Microarray Analysis (CMA) for Prenatal Diagnosis (see policy guidelines for conventional karyotype and FISH testing)

I. Chromosome microarray analysis (81229) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when **both** of the following criteria are met:
   A. The member meets **any** of the following:
      1. A fetus with one or more major structural abnormalities (see definitions) on ultrasound
      2. Advanced maternal age (age 35 years or older at delivery)
      3. An abnormal prenatal screening test (e.g., high risk non-invasive prenatal screening, abnormal first trimester or quadruple screen, or antenatal soft markers on ultrasound)
      4. A parental carrier of a chromosome rearrangement or abnormality
      5. A member with a prior pregnancy with a chromosome abnormality
   B. The test has been ordered by or 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 obstetrician-gynecologist (OB-GYN)
      4. A board-certified genetic counselor
      5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology

II. Chromosomal microarray analysis (CMA) (81229) or conventional karyotype analysis for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications.

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

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Chromosomal Microarray Analysis (CMA) For Pregnancy Loss

III. Chromosomal microarray analysis (81229) on products of conception (POC) may be considered **medically necessary** as an alternative to conventional karyotype analysis when the member meets **one** of the following:
   A. Has a pregnancy loss at 20 weeks of gestation or earlier and the member has a history of prior miscarriage
   B. Has a pregnancy loss after 20 weeks of gestation with or without a history of miscarriage

IV. Chromosome microarray analysis (81229) on products of conception (POC) is considered **investigational** for all other indications.

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Exome Or Genome Sequencing For Pregnancy Loss

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

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Prenatal Diagnosis For Single Gene Disorders

VI. Prenatal diagnosis for single-gene disorders (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, 81256, 81257, 81258, 81259, 81260, 81269, 81271, 81274, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 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 **both** of the following criteria are met:
   A. The member has documentation of meeting **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 (or one known carrier if other parent is unavailable)
      3. One biological parent is suspected or known to be a carrier of an X-linked condition
      4. The member has a previous affected child with a genetic condition and germline mosaicism is possible
   B. The test has been ordered by or 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

VII. Prenatal diagnosis for single-gene disorders (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, 81256, 81257, 81258, 81259, 81260, 81269, 81271, 81274, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81337, 81343, 81344, 81361, 81362, 81363, 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*, Huntington disease, etc.) is considered **not medically necessary**.

VIII. Prenatal diagnosis for single-gene disorders (e.g.,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, 81256, 81257, 81258, 81259, 81260, 81269, 81271, 81274, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS,, is considered **investigational** for **any** of the following:

A. Variants of unknown significance (VUS)
B. All other indications not specified above

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Prenatal Diagnosis For Noonan Spectrum Disorders/Rasopathies

IX. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81442) may be considered **medically necessary** when **all** of the following criteria are met:
   A. The member meets **one** of the following:
      1. The member's current pregnancy has an ultrasound finding of increased nuchal translucency or cystic hygroma in the first trimester
      2. The member's current pregnancy has a heart defect (e.g., pulmonary valve stenosis, atrioventricular septal defect, coarctation of the aorta, hypertrophic cardiomyopathy, atrial septal defect, etc.) and a lymphatic anomaly (e.g., edema, hydrops, pleural effusion, polyhydramnios, etc.) in the second trimester
   B. The member's current pregnancy has had a normal karyotype and/or microarray
   C. The panel being ordered includes, at a minimum, the following genes: *BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1*
   D. The panel has been ordered by or 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 OB-GYN
      4. A board-certified genetic counselor
      5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology

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

Note: Prenatal diagnosis for Noonan spectrum or other rasopathy for a pregnancy with no ultrasound findings whose parent has a mutation associated with Noonan or other rasopathy would follow the criteria for Prenatal Diagnosis of Single Gene Disorders

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Prenatal Diagnosis For Skeletal Dysplasias

XI. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479) may be considered **medically necessary** when **all** 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 member's current pregnancy has had a normal karyotype and/or microarray
C. The panel being ordered includes, at a minimum, the following genes: *ALPL*, *COL1A1*, *COL1A2*, *COL2A1*, *FGFR3*, *INPPL1*, *NKX3-2*, *SLC26A2*, *SOX9*, *TRIP11*
D. The panel has been ordered by or 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 OB-GYN
   4. A board-certified genetic counselor
   5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology

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

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Prenatal Diagnosis Via Exome Sequencing

XIII. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81417, 81265) 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 (see definitions)
   B. The member's current pregnancy has had a karyotype and/or microarray performed and the results were negative/normal
   C. The panel has been ordered by or 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 OB-GYN
      4. A board-certified genetic counselor
      5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology

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

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Prenatal Diagnosis Using Genome Sequencing

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

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

Policy Guidelines

Karyotype (88267, 88269, 88235, 88280, 88291 is allowed as an initial step for prenatal diagnosis. CMA can be done as an alternative or in addition to karyotyping.

FISH (88271, 88275) is allowed in addition to karyotype or CMA.

Notes and Definitions

1. **Major malformations** are structural defects that have a significant effect on function or appearance. They may be lethal or associated with possible survival with severe or moderate immediate or long-term morbidity. Examples by organ system include:
   - Genitourinary: renal agenesis (unilateral or bilateral), hypoplastic/cystic kidney
   - Cardiovascular: complex heart malformations (such as pulmonary valve stenosis, tetralogy of fallot, transposition of the great arteries, coarctation of the aorta, hypoplastic left heart syndrome
   - Musculoskeletal: osteochondrodysplasia/osteogenesis imperfecta, clubfoot, craniosynostosis
   - Central nervous system: anencephaly, hydrocephalus, myelomeningocele
   - Body wall: omphalocele/gastroschisis
   - Respiratory: cystic adenomatoid lung malformation
2. **Amniocentesis** is a procedure in which a sample of amniotic fluid is removed from the uterus for prenatal diagnostic testing.
3. **Chorionic Villi Sampling (CVS)** is a procedure where a sample of chorionic villi is removed from the placenta for prenatal diagnostic testing.
4. **Percutaneous Umbilical Cord Blood Sampling (PUBS)** is a procedure where a sample of fetal blood is extracted from the vein in the umbilical cord.

Clinical Considerations

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

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

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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.

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. *(to be published)*
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to prenatal diagnostic or pregnancy loss genetic testing that is not specifically discussed in this or other non-general policies. *(to be published)*

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

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Chromosomal Microarray Analysis for Prenatal Diagnosis

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

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

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

ACOG and SMFM (2016) published the joint practice bulletin No. 162 and made the following considerations and recommendations regarding prenatal diagnostic testing for genetic disorders:
The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

- "Chromosomal microarray analysis has been found to detect a pathogenic (or likely pathogenic) copy number variant in approximately 1.7% of patients with a normal ultrasound examination result and a normal karyotype, and it is recommended that chromosomal microarray analysis be made available to any patient choosing to undergo invasive diagnostic testing."
- "Early amniocentesis (before 14 weeks of gestation) is not recommended."
- "When structural abnormalities are detected by prenatal ultrasound examination, chromosomal microarray will identify clinically significant chromosomal abnormalities in approximately 6% of the fetuses that have a normal karyotype. For this reason, chromosomal microarray analysis should be recommended as the primary test (replacing conventional karyotype) for patients undergoing prenatal diagnosis for the indication of a fetal structural abnormality detected by ultrasound examination. If a structural abnormality is strongly

suggestive of a particular aneuploidy in the fetus (e.g., duodenal atresia or an atrioventricular heart defect, which are characteristic of trisomy 21), karyotype with or without FISH may be offered before chromosomal microarray analysis."

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

- "An abnormal FISH result should not be considered diagnostic. Therefore, clinical decision making based on information from FISH should include at least one of the following additional results: confirmatory traditional metaphase chromosome analysis or chromosomal microarray, or consistent clinical information (such as abnormal ultrasonographic findings or a positive screening test result for Down syndrome or trisomy 18)."

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

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

Conventional Chromosome Analysis for Prenatal Diagnosis

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

A recent 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."

"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."

Chromosomal Microarray Analysis for Pregnancy Loss

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

Because of the advantages chromosomal microarray has over karyotyping (chromosome analysis), ACOG and SMFM support the following for pregnancy loss in their 2016 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."

Conventional Chromosome Analysis for Pregnancy Loss

American Society for Reproductive Medicine (ASRM)

According to the ASRM's 2012 statement, recurrent pregnancy loss (RPL) is defined as occurring "after two consecutive clinical pregnancy losses….Karyotypic analysis of products of conception may be useful in the setting of ongoing therapy for RPL."

Prenatal Diagnosis for Single-Gene Disorders

National Society of Genetic Counselors (NSGC)

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

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

Huntington's Disease Society of America

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

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

Prenatal Diagnosis for Skeletal Dysplasia

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

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

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."

- "Pretest counseling is ideally provided by a genetics professional during which the types of variants that may be returned in a laboratory report for all tested family members would be reviewed. Both pretest counseling"
- "With the use of prenatal ES, the turnaround time has to be rapid to maintain all aspects of reproductive choice. A rapid turnaround time has been demonstrated in the postnatal setting for critical genetic diagnoses in a pediatric and neonatal setting. Laboratories offering prenatal ES should have clearly defined turnaround times for this time-sensitive test."

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

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. Test and Technology Transfer Committee, American College of Medical Genetics, 9650 Rockville Pike, Bethesda, MD 20814-3998, United States.. Technical and clinical assessment of fluorescence in situ hybridization: an ACMG/ASHG position statement. I. Technical considerations. Test and Technology Transfer Committee. Genet Med. 2000;2(6):356-361. doi:10.1097/00125817-200011000-00011
5. 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
6. Leach NT, Wilson Mathews DR, Rosenblum LS, Zhou Z, Zhu H, Heim RA. Comparative assessment of gene-specific variant distribution in prenatal and postnatal cohorts tested for Noonan syndrome and related conditions [published correction appears in Genet Med. 2018 Jul 26;:]. Genet Med. 2019;21(2):417-425. doi:10.1038/s41436-018-0062-0
7. Leach NT, Wilson Mathews DR, Rosenblum LS, Zhou Z, Zhu H, Heim RA. Correction: Comparative assessment of gene-specific variant distribution in prenatal and postnatal cohorts tested for Noonan syndrome and related conditions. Genet Med. 2019;21(7):1670. doi:10.1038/s41436-018-0128-z
8. 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
9. 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
10. Donley G, Hull SC, Berkman BE. Prenatal whole genome sequencing: just because we can, should we?. Hastings Cent Rep. 2012;42(4):28-40. doi:10.1002/hast.50
11. "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.
12. "Genetic Testing Protocol for Huntington's Disease". Huntington's Disease Society of America. http://hdsa.org/wp-content/uploads/2015/02/HDSA-Gen-Testing-Protocol-for-HD.pdf. 2016. Accessed October 27, 2020.
13. 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
14. Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG) [published online ahead of print, 2021 May 20]. Genet Med. 2021;10.1038/s41436-021-01171-4. doi:10.1038/s41436-021-01171-4
15. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG) [published online ahead of print, 2021 May 20]. Genet Med. 2021;10.1038/s41436-021-01172-3. doi:10.1038/s41436-021-01172-3
16. 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

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason for test
  - Type/name of test
  - Family history including known variant or carrier status of parents
  - Documentation of high risk pregnancy and why it is high risk
  - Evidence-based support for genetic test or specific gene(s) of interest

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

- Laboratory report(s)

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®	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

Type	Code	Description
		(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)
	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
	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)

Type	Code	Description
	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
	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
	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)
	81256	HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)
	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)

Type	Code	Description
	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
	81271	HTT (huntingtin) (e.g., Huntington disease) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81274	HTT (huntingtin) (e.g., Huntington disease) gene analysis; characterization of alleles (e.g., expanded size)
	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
	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
	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)
	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

Type	Code	Description
	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)
	81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
	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
	88230	Tissue culture for non-neoplastic disorders; lymphocyte
	88235	Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells
	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
	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
	88271	Molecular cytogenetics; DNA probe, each (e.g., FISH)
	88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
	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.

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	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Invasive Prenatal (Fetal) Diagnostic Testing 2.04.116 **Policy Statement:** **Chromosomal Microarray Testing** I. In individuals who are undergoing invasive diagnostic prenatal (fetal) testing, chromosome microarray testing may be considered **medically necessary** as an alternative to karyotyping (see Policy Guidelines).	**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 (see policy guidelines for conventional karyotype and FISH testing)** I. Chromosome microarray analysis (81229) for prenatal diagnosis via amniocentesis, CVS, or PUBS may be considered **medically necessary** when **both** of the following criteria are met: A. The member meets **any** of the following: 1. A fetus with one or more major structural abnormalities (see definitions) on ultrasound 2. Advanced maternal age (age 35 years or older at delivery) 3. An abnormal prenatal screening test (e.g., high risk non-invasive prenatal screening, abnormal first trimester or quadruple screen, or antenatal soft markers on ultrasound) 4. A parental carrier of a chromosome rearrangement or abnormality 5. A member with a prior pregnancy with a chromosome abnormality B. The test has been ordered by or 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 obstetrician-gynecologist (OB-GYN) 4. A board-certified genetic counselor 5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology II. Chromosomal microarray analysis (CMA) (81229) or conventional karyotype analysis for prenatal diagnosis via amniocentesis, CVS, or PUBS is considered **investigational** for all other indications. back to top

POLICY STATEMENT	
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	Note: Current guidelines recommend that chromosome microarray analysis (CMA) be performed as the primary test for patients undergoing prenatal diagnosis when the fetus has one or more major structural abnormalities identified by ultrasound examination (see Background and Rationale for more information). back to top **Chromosomal Microarray Analysis (CMA) For Pregnancy Loss** III. Chromosomal microarray analysis (81229) on products of conception (POC) may be considered **medically necessary** as an alternative to conventional karyotype analysis when the member meets **one** of the following: A. Has a pregnancy loss at 20 weeks of gestation or earlier and the member has a history of prior miscarriage B. Has a pregnancy loss after 20 weeks of gestation with or without a history of miscarriage IV. Chromosome microarray analysis (81229) on products of conception (POC) is considered **investigational** for all other indications. back to top **Exome Or Genome Sequencing For Pregnancy Loss** V. Prenatal diagnosis on products of conception (POC) using exome or genome sequencing (81265, 81415, 81416, 88235) is considered **investigational**. back to top
Single-Gene Disorders II. Invasive diagnostic prenatal (fetal) testing for molecular analysis for single-gene disorders may be considered **medically necessary** when **all** of the following criteria have been met: A. A pregnancy has been identified as being at high risk for **any** of the following:	**Prenatal Diagnosis For Single Gene Disorders** VI. Prenatal diagnosis for single-gene disorders (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, 81256, 81257, 81258, 81259, 81260, 81269, 81271, 81274, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81337, 81343, 81344,

POLICY STATEMENT	
BEFORE **Red font: Verbiage removed**	**AFTER** **Blue font: Verbiage Changes/Additions**
1. Autosomal dominant conditions, at least one of the parents has a known pathogenic variant. 2. Autosomal recessive conditions in **either** of the following: a. Both parents are suspected to be carriers or are known to be carriers b. One parent is clinically affected and the other parent is suspected to be or is a known carrier 3. X-linked conditions: A parent is suspected to be or is a known carrier B. The natural history of the disease is well-understood, and there is a reasonable likelihood that the disease is one with high morbidity in the homozygous or compound heterozygous state C. Any variants have high penetrance D. The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood E. An association of the marker with the disorder has been established III. If the above criteria for molecular analysis of single-gene disorders are not met, invasive diagnostic prenatal (fetal) testing is considered **investigational**. **Next-Generation Sequencing** IV. The use of next-generation sequencing in the setting of invasive prenatal testing is considered **investigational**.	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 **both** of the following criteria are met: A. The member has documentation of meeting **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 (or one known carrier if other parent is unavailable) 3. One biological parent is suspected or known to be a carrier of an X-linked condition 4. The member has a previous affected child with a genetic condition and germline mosaicism is possible B. The test has been ordered by or 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 VII. Prenatal diagnosis for single-gene disorders (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, 81256, 81257, 81258, 81259, 81260, 81269, 81271, 81274, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81337, 81343, 81344, 81361, 81362, 81363, 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*, Huntington disease, etc.) is considered **not medically necessary**.

POLICY STATEMENT	
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	VIII. Prenatal diagnosis for single-gene disorders (e.g.,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, 81256, 81257, 81258, 81259, 81260, 81269, 81271, 81274, 81284, 81285, 81286, 81289, 81290, 81303, 81312, 81330, 81331, 81332, 81337, 81343, 81344, 81361, 81362, 81363, 81364, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 88235, 81265), via amniocentesis, CVS, or PUBS,, is considered **investigational** for **any** of the following: C. Variants of unknown significance (VUS) D. All other indications not specified above back to top **Prenatal Diagnosis For Noonan Spectrum Disorders/Rasopathies** IX. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81442) may be considered **medically necessary** when **all** of the following criteria are met: A. The member meets **one** of the following: 1. The member's current pregnancy has an ultrasound finding of increased nuchal translucency or cystic hygroma in the first trimester 2. The member's current pregnancy has a heart defect (e.g., pulmonary valve stenosis, atrioventricular septal defect, coarctation of the aorta, hypertrophic cardiomyopathy, atrial septal defect, etc.) and a lymphatic anomaly (e.g., edema, hydrops, pleural effusion, polyhydramnios, etc.) in the second trimester B. The member's current pregnancy has had a normal karyotype and/or microarray C. The panel being ordered includes, at a minimum, the following genes: *BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, SOS1*

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	D. The panel has been ordered by or 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 OB-GYN 4. A board-certified genetic counselor 5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology X. Prenatal diagnosis for Noonan spectrum disorders/RASopathies, via amniocentesis, CVS, or PUBS, using a Noonan syndrome panel (81404, 81405, 81406, 81442) is considered **investigational** for all other indications. **Note**: Prenatal diagnosis for Noonan spectrum or other rasopathy for a pregnancy with no ultrasound findings whose parent has a mutation associated with Noonan or other rasopathy would follow the criteria for Prenatal Diagnosis of Single Gene Disorders back to top **Prenatal Diagnosis For Skeletal Dysplasias** XI. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479) may be considered **medically necessary** when **all** 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

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	B. The member's current pregnancy has had a normal karyotype and/or microarray C. The panel being ordered includes, at a minimum, the following genes: *ALPL*, *COL1A1*, *COL1A2*, *COL2A1*, *FGFR3*, *INPPL1*, *NKX3-2*, *SLC26A2*, *SOX9*, *TRIP11* D. The panel has been ordered by or 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 OB-GYN 4. A board-certified genetic counselor 5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology XII. Prenatal diagnosis for skeletal dysplasias, via amniocentesis, CVS, or PUBS, using a skeletal dysplasia panel (81404, 81405, 81408, 81479) is considered **investigational** for all other indications. back to top **Prenatal Diagnosis Via Exome Sequencing** XIII. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81417, 81265) 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 (see definitions) B. The member's current pregnancy has had a karyotype and/or microarray performed and the results were negative/normal C. The panel has been ordered by or 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 OB-GYN

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	4. A board-certified genetic counselor 5. An advanced practice practitioner in genetics or maternal-fetal medicine/perinatology XIV. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using exome sequencing (81415, 81416, 81265) is considered **investigational** for all other indications. back to top **Prenatal Diagnosis Using Genome Sequencing** XV. Prenatal diagnosis, via amniocentesis, CVS, or PUBS, using genome sequencing (81425, 81426, 81427, 88235, 81265) is considered **investigational**.