Medical Coverage Policy

Effective Date.....12/15/2023
Next Review Date.....12/15/2024
Coverage Policy Number..... 0514

Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis

Table of Contents

Related Coverage Resources

Genetics
Genetic Testing Collateral File
Infertility Services
Recurrent Pregnancy Loss: Diagnosis and Treatment

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers

must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses genetic testing for germline variant reproductive carrier screening and prenatal diagnosis. Germline gene variants occur in the egg and sperm cells, also known as the germ cells. These variants are inherited, that is, passed down in families by blood relatives.

Reproductive carrier screening and prenatal diagnosis refer to testing for the presence of certain germline gene variants that are associated with disease or a risk of disease in an individual's offspring and descendants, before or after pregnancy has occurred. This type of testing allows for reproductive planning.

Coverage Policy

Many benefit plans limit coverage of genetic testing, genetic counseling and infertility services. Please refer to the applicable benefit plan language to determine benefit availability and terms, conditions and limitations of coverage for the services discussed in this Coverage Policy.

For additional information regarding coverage for specific genetic tests, please refer to the Genetic Testing Collateral File.

GENETIC COUNSELING

Pre-and post-test genetic counseling is considered medically necessary for EITHER of the following:

- an individual undergoing genetic testing
- an individual who is a potential candidate for genetic testing

by ANY of the following:

- an independent Board-Certified or Board-Eligible Medical Geneticist
- an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself)
- a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test)

GERMLINE CARRIER TESTING FOR FAMILIAL DISEASE

Preconception or prenatal carrier testing for an individual who has the capacity and intention to reproduce is considered medically necessary when ANY of the following criteria is met:

- There is an identified pathogenic or likely pathogenic variant in a blood relative
- EITHER of the following criteria is met:
  - an individual's reproductive partner is a known carrier of a disease-causing pathogenic or likely pathogenic variant in a recessively inherited condition
  - a genetic diagnosis has been confirmed in an affected relative, AND the affected relative has not had genetic testing and is unavailable for testing

When ANY of the above criteria is met, preconception or prenatal carrier testing is considered medically necessary for the following indications (list may not be all inclusive):

Nuclear mitochondrial genes	**Sickle cell disease**
Muscular dystrophies (DMD, BMD, EDMD, DM1, DM2, SM)	**Alpha and beta thalassemia**
Fragile X syndrome	**Gaucher disease**
Rett syndrome	**Niemann-Pick disease**
PTEN-related disorders	**Canavan disease**
Von Hippel-Lindau disease	**Tay-Sachs disease**
Long QT syndrome	**DFNB1 nonsyndromic hearing loss and deafness**
Retinoblastoma	**Huntington disease**
21-hydroxylase deficiency	**Cystic fibrosis**

Preconception or prenatal genetic testing of a prospective biologic female parent for Fragile X (i.e., FMR1) gene mutations is considered medically necessary for EITHER of the following indications:

- family history of unexplained intellectual disability or developmental delay, or autism in a blood relative
- personal or family history of premature ovarian insufficiency

Preconception or prenatal carrier testing for spinal muscular atrophy by SMN1 gene variant analysis (CPT code 81329) for the purpose of reproductive screening is considered medically necessary when the individual has the capacity and intention to reproduce and testing has not been previously performed.

Preconception or prenatal carrier testing for cystic fibrosis (CF) with targeted variant analysis of CFTR gene variants (CPT code 81220) as described by the American College of Medical Genetics (ACMG) is considered medically necessary for a prospective biologic parent with the capacity and intention to reproduce and testing has not previously been performed.

Preconception or prenatal carrier testing for hemoglobinopathies (i.e., thalassemias, sickle cell disease) (CPT codes 81257, 81361) is considered medically necessary when

the individual has the capacity and intention to reproduce and testing has not been previously performed.

Preconception or prenatal carrier testing for a prospective biologic parent of Ashkenazi Jewish (AJ) descent is considered medically necessary for the conditions specified by the American College of Medical Genetics, including but not limited to the following:

- familial dysautonomia (CPT code 81260)
- Tay-Sachs disease (CPT code 81255)
- Canavan disease (CPT code 81200)
- Fanconi anemia group C (CPT code 81242)
- Niemann-Pick disease, type A (CPT code 81330)
- Bloom syndrome (CPT code 81209)
- Mucolipidosis IV (CPT code 81290)
- Gaucher disease, type 1 (CPT code 81251)
- targeted panel testing for variants found in an individual of AJ descent

Reproductive carrier screening based on the general population risk, other than conditions noted above, is considered not medically necessary.
Reproductive carrier screening for nonmedical traits (e.g., eye color, hair color) is considered not medically necessary.

A multigene reproductive carrier screening panel with ≥ 15 genes to predict the risk of severe inherited disease is not covered or reimbursable.

PREIMPLANTATION GENETIC TESTING OF AN EMBRYO

When the specific criteria noted below are met, Cigna will cover the embryo biopsy procedure to obtain the cell and genetic testing associated with preimplantation genetic testing (PGT) under the core medical benefits of the plan.

The embryo biopsy procedure, genetic test and pre-and post-test genetic counseling associated with PGT (PGT for monogenic disorders [PGT-M] or PGT for chromosomal structural rearrangements [PGT-SR]) are considered medically necessary when ALL of the following criteria are met:

- the genetic condition is associated with severe disability or has a lethal natural history
- the proposed test is medically necessary for the diagnosis(es)/indication(s) listed and there is sufficient evidence to demonstrate improved health outcomes
- the results of the genetic test will impact clinical decision-making and clinical outcome when ANY of the following criteria is met:
    - both biologic parents are carriers of a single gene autosomal recessively-inherited disorder
    - one biologic parent is a known carrier of a single gene autosomal dominantly-inherited disorder or a single x-linked disorder
    - one biologic parent is a translocation carrier

When the above criteria are met, PGT is considered medically necessary for the following indications (list may not be all inclusive):

Nuclear mitochondrial genes	**Sickle cell disease**
Muscular dystrophies (DMD, BMD, EDMD, DM1, DM2, SM)	**Alpha and beta thalassemia**

Fragile X syndrome	**Gaucher disease**
Rett syndrome	**Niemann-Pick disease**
PTEN-related disorders	**Canavan disease**
Von Hippel-Lindau disease	**Tay-Sachs disease**
Long QT syndrome	**DFNB1 nonsyndromic hearing loss and deafness**
Retinoblastoma	**Huntington disease**
21-hydroxylase deficiency	**Cystic fibrosis**

PGT for any other indication, including but not limited to the following, is considered experimental, investigational or unproven:

- human leukocyte antigen (HLA) typing of an embryo to identify a future suitable stem-cell tissue or organ transplantation donor
- testing solely to determine if an embryo is a carrier of an autosomal recessively-inherited disorder
- testing for a multifactorial condition
- testing for variants of unknown significance

PGT for testing of an embryo for nonmedical gender selection or nonmedical traits is considered not medically necessary.

PGT-P (polygenic risks scores) is considered not medically necessary.

PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY (PGT-A)

Preimplantation genetic testing for aneuploidy (PGT-A) by any testing methodology (e.g., comparative genetic hybridization [CGH], fluorescence in situ hybridization [FISH], gene sequencing) for any indication, including but not limited to the following indications, is considered not medically necessary:

- advanced maternal age (i.e., ≥ age 35 years)
- repeated in vitro fertilization (IVF) failures
- recurrent spontaneous abortions

PRENATAL GENETIC SCREENING AND TESTING OF A FETUS

Pre- and post-test genetic counseling is recommended for an individual who is considering genetic screening for fetal aneuploidy.

SEQUENCING-BASED NON-INVASIVE PRENATAL TESTING (NIPT)

Sequencing-based non-invasive prenatal testing (NIPT) (CPT® codes 81420, 81507, 0327U) to screen for fetal trisomy 13, 18 and 21 is considered medically necessary in a viable single or twin gestation pregnancy ≥ 10 weeks gestation when testing has not already been performed.

In-network coverage of sequencing-based NIPT screening tests for fetal trisomy 13, 18 and 21 performed in an out of network laboratory is considered not medically necessary since these are available at an in-network laboratory.

Molecular analysis of intact fetal cells (i.e., fetal trophoblast[s] in a maternal sample) is considered experimental, investigational or unproven.

Sequencing-based non-invasive prenatal testing for any other indication, including but not limited to the following, is not covered or reimbursable:

- higher order multiple gestations (e.g. triplets and higher)
- screening for a sex-chromosome aneuploidy
- vanishing twin syndrome
- twin zygosity
- screening for trisomy 7, 9, 16, 22 or other rare autosomal trisomies (RATs)
- screening for microdeletions
- single-gene disorders
- when used to determine genetic cause of miscarriage (e.g., missed abortion, incomplete abortion)
- screening for nonmedical traits (e.g., biologic sex)

INVASIVE PRENATAL TESTING OF A FETUS

Invasive prenatal testing of a fetus for a familial variant is considered medically necessary when the results of genetic testing will impact clinical decision-making and clinical outcome and ANY of the following criteria are met:

- the mother is a carrier of an X-linked condition
- both biologic parents are carriers of an autosomal recessively-inherited disorder OR the mother is a known carrier of an autosomal recessively-inherited disorder and the father's status is unknown and unavailable
- one parent is the carrier of an autosomal dominantly–inherited disorder

Prenatal testing of a fetus is considered medically necessary when abnormal findings have been identified on ultrasound.

Prenatal reproductive evaluation of a fetus is considered medically necessary using EITHER of the following tests:

- comparative genomic hybridization (CGH) testing (chromosomal microarray analysis) (CPT code 81228, 81229)
- genome wide copy number variant analysis/low pass WGS (81349)

for ANY of the following indications:

- a woman is undergoing invasive prenatal genetic testing
- intrauterine fetal loss at ≥ 20 weeks or stillbirth
- intrauterine fetal loss with a documented structural anomaly at any gestation age

Prenatal molecular testing of a fetus for familial variants of unknown significance (VUS) is not covered or reimbursable.

GERMLINE MUTATION REPRODUCTIVE GENETIC TESTING FOR RECURRENT PREGNANCY LOSS

The following genetic tests are considered medically necessary for the evaluation of recurrent pregnancy loss (i.e., two or more pregnancy losses):

- peripheral-blood karyotyping of the biologic parents to detect balanced chromosomal abnormalities
- karyotyping or comparative genomic hybridization (CGH) testing (chromosomal microarray analysis) (CPT code 81228, 81229) of the products of conception at the time of the second loss

EITHER of the following genetic tests for recurrent pregnancy loss is considered not medically necessary:

- molecular testing for highly skewed X-inactivation patterns
- molecular cytogenetic testing using comparative genomic hybridization (CGH) testing for chromosomal analysis (e.g., parental blood)

Methylene tetrahydrofolate reductase (MTHFR) testing for recurrent pregnancy loss is not covered or reimbursable.

Single gene mutation analysis, including for ANY of the following genes is considered not medically necessary in the evaluation of recurrent pregnancy loss:

- F7 (coagulation factor VII [serum prothrombin conversion accelerator] R353Q variant)
- F13B (coagulation factor XIII, B polypeptide, V34L variant)
- PAI-1 gene testing

GERMLINE MUTATION REPRODUCTIVE GENETIC TESTING FOR INFERTILITY

The following services are considered medically necessary when performed solely to establish the underlying etiology of infertility:

- genetic testing for cystic fibrosis in males with either congenital bilateral absence of vas deferens or azoospermia or severe oligospermia (i.e., < five million sperm/millimeter) with palpable vas deferens
- karyotyping for chromosomal abnormalities in males with nonobstructive azoospermia or severe oligospermia
- Y-chromosome microdeletion testing in males with nonobstructive azoospermia or severe oligospermia
- Sperm penetration assay (hamster penetration test, zona free hamster oocyte test) for those with male factor infertility, who are considering in vitro fertility (IVF) cycles and intracytoplasmic sperm (ICSI)

In the absence of a diagnosis of infertility, Cigna considers IVF services associated with preimplantation genetic diagnosis to be not medically necessary.

The following tests are not covered or reimbursable:

- sperm DNA integrity testing (e.g., Sperm Chromatin Structure assay [SCSA], TUNEL assay, Comet assay, Human Sperm Activation Assay [HSAA], Sperm DNA Decondensation™)

General Background

Genetic Counseling

Genetic counseling is defined as the process of helping individuals understand and adapt to the medical, psychological and familial indications of genetic contributions to disease. Genetic counseling services span the life cycle from preconception counseling to infertility evaluation, prenatal genetic screening and diagnosis, and include predisposition evaluation and genetic diagnosis (National Society of Genetic Counselors [NSGC]; Edwards, 2010). Genetic counseling is recommended both pre-and post-genetic test to interpret family and medical histories to assess the chance of disease occurrence and recurrence, educate regarding inheritance, testing, management prevention and resources, and counsel to promote informed choices and adaptation to risk or condition (NSGC). A variety of genetics professionals provide these services: Board-Certified or Board-Eligible Medical Geneticists, an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor, and genetic nurses credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC). Individuals should not be employed by a commercial genetic testing laboratory, although counseling services by these individuals are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself.

Germline Carrier Testing for Familial Disease

A genetic test is defined as the analysis of human deoxyribonucleic acid (DNA), ribonucleic acid (RNA), chromosomes, proteins, and certain metabolites in order to detect mutations or alterations related to an inherited disorder; that is, one passed down by blood relatives. Genetic tests are often performed for the purpose of reproductive carrier screening and prenatal diagnosis to allow for reproductive planning. These terms refer to a search for certain genotypes that are already associated with disease or predisposition which may lead to disease in an individual's offspring and descendants, or may produce other variations not known to be associated with disease. Genetic testing for reproductive carrier screening and prenatal diagnosis may be appropriate in certain clinical scenarios, including carrier testing for familial disease, ethnic carrier screening, preimplantation genetic diagnostic testing of an embryo, prenatal testing and screening, recurrent pregnancy loss and infertility. Preconception or prenatal testing of a fetus allows for informed reproductive choices.

Certain principles apply to genetic testing to determine the presence of gene mutations known to cause heritable disease within a blood-related family. It is generally appropriate to utilize a stepwise process for preconception and prenatal carrier testing unless timing of the testing will limit reproductive choice because of gestational age. Published consensus guidelines from the American College of Medical Genetics and Genomics (ACMG, 2006) and the American Congress of Obstetricians and Gynecologists (ACOG, 2017) support carrier testing for familial disease. Carrier testing, including testing for a known familial mutation, targeted mutation analysis, gene sequencing, duplication/deletion testing or gene dose analysis methods is established as a means to improve health outcomes in selected individuals with risk of a familial disease. Such testing allows prospective parents to make informed reproductive choices.

Disorders for which preconception carrier testing may be appropriate include, but are not limited to the following:

Nuclear mitochondrial genes	21-hydroxylase deficiency
Muscular dystrophies (DMB, BMD, EDMD, DM1, DM2, SM)	Sickle cell disease
Fragile X syndrome	Alpha and beta Thalassemia
Rett syndrome	Gaucher disease
PTEN-related disorders	Niemann-Pick disease
Von Hippel-Lindau disease	Canavan disease

Long QT syndrome	Tay-Sachs disease
Retinoblastoma	DFNB1 nonsyndromic hearing loss and deafness
Huntington disease	Cystic fibrosis
Spinal Muscular Atrophy (SMA)	

Genetic testing for non-medical traits such as hair and eye color does not result in improved health outcomes and such testing is not considered to have clinical utility for these indications.

Certain disorders are known to occur with greater frequency in defined ethnic populations compared to frequency in the general population. The ACMG (2008) and ACOG (2017) published guidelines to support preconception and prenatal carrier screening for these indications. Genetic testing using targeted mutation panels is considered the standard of care for the following disorders:

- familial dysautonomia (CPT code 81260)
- Tay-Sachs disease (CPT code 81255)
- Canavan disease (CPT code 81200)
- Fanconi anemia group C (CPT code 81242)
- Niemann-Pick disease, type A (CPT code 81330)
- Bloom syndrome (CPT code 81209)
- Mucolipidosis IV (CPT code 81290)
- Gaucher disease, type 1 (CPT code 81251)

Such testing is considered standard of care in clinical practice for certain defined germline disorders; however, in the absence of clinical features which would suggest one of these disorders, the clinical utility of gene sequencing as a testing approach has not been established.

Large pan-ethnic expanded carrier screening panels are now available which may include hundreds of genes, and are intended to be used for general population carrier screening. There are no standard guidelines regarding which disease genes and pathogenic or likely pathogenic variants to include on an expanded carrier screening panel of this size. These panels often include diseases that are present with increased frequency in specific populations, as well as a large number of diseases for which the carrier frequency in the general population is low in the absence of a known family history.

Multiple professional societies have called for guidelines to be developed that would limit genes on these panels based on standard criteria, such as only including severe, childhood-onset genetic diseases, and only genes for which pathogenic or likely pathogenic variant frequencies are known and prognosis can be predicted based on genotype (Edwards, et al., 2015; Grody, et al., 2013). There is insufficient evidence to support improved health and/or pregnancy outcomes with the use of large multigene reproductive carrier screening panels to predict the risk of severe inherited disease.

ACMG (2020) published consensus guidelines to support targeted mutation analysis of 23 CFTR mutations for testing of individuals for whom the risk of cystic fibrosis is a concern. In an effort to standardize the laboratory approach to screening, the Subcommittee on Cystic Fibrosis Screening, the American College of Medical Genetics and Genomics (ACMG) recommends the use of a pan-ethnic panel that includes all mutations with an allele frequency ≥ 0.1% in the general United States (U.S.) population. Initially, 25 mutations were included in the standard core mutation analysis of the CFTR gene; however, a 2004 update to the ACMG cystic fibrosis carrier screening statement recommended no additions and two deletions (I148T, 1078delT). The ACMG mutation

panel is considered the standard test for population-based carrier testing and is performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories.

Targeted mutation analysis for common deletion or gene variants (i.e., HBB, HBA1, HBA2) for thalassemia and sickle cell disease is supported by published professional society guidelines and peer-reviewed evidence. Gene sequencing and deletion/duplication studies may be appropriate to identify mutations if results of targeted mutation studies are negative or use of a stepwise approach limits reproductive options due to gestational age.

Consensus support for screening for all heritable conditions in the general population is lacking. According to the ACMG (2019), the approach to genetic counseling and testing for the different phenotypes has not yet been addressed on a population screening level. Except where identified as clinically useful elsewhere in this Coverage Policy, carrier screening in the general population in the absence of definitive clinical features does not impact clinical decision-making or improve health outcomes. Therefore, clinical utility for this indication has not been established.

Professional Societies/Organizations
For a summary of professional society recommendations/guidelines (including Use Outside of the US) regarding germline carrier testing for familial disease, please see Appendix.

Preimplantation Genetic Testing of an Embryo
Preimplantation genetic diagnosis (PGD), now referred to as preimplantation genetic testing (PGT) is clinically useful when a genetic disorder is associated with a severe disability or has a lethal natural history PGT would be appropriate when reproductive partners are carriers of a single gene autosomal recessively-inherited disorder or one partner is a known carrier of an autosomal dominant or x-linked heritable disorder and the results will impact clinical decision-making. PGD may be appropriate for the following indications (this list may not be all-inclusive):

Nuclear mitochondrial genes	Sickle cell disease
Muscular dystrophies (DMD, BMD, EDMD, DM1, DM2, SM	Alpha and beta thalassemia
Fragile X syndrome	Gaucher disease
Rett syndrome	Niemann-Pick disease
PTEN-related disorders	Canavan disease
Von Hippel-Lindau disease	Tay-Sachs disease
Long QT syndrome	DFNB1 nonsyndromic hearing loss and deafness
Retinoblastoma	Huntington disease
21-hydroxylase deficiency	Cystic fibrosis

Use of PGD in multifactorial conditions and for testing for variants of unknown significance does not result in improved health outcomes. The clinical utility of PGD has not been established for these indications.

PGD used solely to determine if an embryo is a carrier of an autosomal recessively inherited disorder is not supported in published professional society/organization guidelines. PGD used solely to identify potential suitable stem-cell tissue or solid organ transplantation donor is not considered standard of care for this indication. PGD has also been proposed as a means to detect chromosomal rearrangements (e.g., translocations) in order to decrease the rate of spontaneous abortions. However, at this time there are insufficient data to support preimplantation genetic screening for unexplained recurrent miscarriage.

Although testing for a known familial mutation is an accepted testing strategy for PGD, the role of gene sequencing has not been established in the published peer reviewed scientific literature. Testing of an embryo for nonmedical gender selection or nonmedical traits, such as hair and eye color does not result in improved health outcomes and clinical utility for this indication has not been established.

A polygenic risk score is an estimate of an individual's genetic risk for a specific polygenic phenotype that is derived from weights of alleles from hundreds to thousands of loci. A polygenic risk score informs about an individual's relative risk compared to the remainder of the population. Published peer-reviewed scientific literature for polygenic risk scores is lacking and insufficient to support coverage.

Professional Societies/Organizations
For a summary of professional society recommendations/guidelines (including Use Outside of the US) regarding preimplantation genetic testing of an embryo, please see Appendix.

Preimplantation Genetic Screening for Aneuploidy
PGD has been used for the screening of embryos for common aneuploidies in couples undergoing IVF procedures for infertility with a history of recurrent pregnancy loss, repeated IVF failures and/or advanced maternal age. When PGD is performed for any of these indications, it has been referred to as PGD-A, or as preimplantation genetic screening (PGS). Outcome measures used in PGD-A include pregnancy rates (e.g., for recurrent pregnancy loss, and live birth rates). The error rate of aneuploidy detection has been reported to be as high as 15%. This use of PGD is a screening procedure to detect those aneuploidies most commonly observed after birth or in miscarriages (e.g., involving detection of chromosomes X, Y, 13, 16, 18, 21, and 22). Together, these chromosomes account for 95% of all chromosomal abnormalities.

Additional well-designed, multicenter studies are needed before the role of preimplantation genetic screening (PGS) for aneuploidy can be established. There is insufficient evidence and professional guidance in the published, peer-reviewed scientific literature to support PGD for: human leukocyte antigen (HLA) - matching, screening of common aneuploidy or chromosomal translocations as a method to improve live birth rates, to reduce the risk of pregnancy loss in women of advanced maternal age, or for late-onset disorders. The clinical treatment utility of PGD for late-onset conditions has not been clearly delineated. Published consensus guidelines from ACOG (2009) do not support PGS as a genetic screening test for common aneuploidy. The clinical utility for this indication has not been established.

Literature Review
Studies evaluating the effectiveness of PGS include prospective nonrandomized and randomized controlled trials. In general study results have suggested that PGS does not improve pregnancy outcomes for young women with recurrent implantation failure or those of advanced maternal age (Rubio, et al., 2013; DeBrock, et al., 2010; Meyer, et al., 2009; Hardarson, et al., 2008; Yakin, et al., 2008; Mastenbroek, et al., 2007; Staessen, et al., 2004).

Professional Societies/Organizations
For a summary of professional society recommendations/guidelines (including Use Outside of the US) regarding preimplantation genetic screening for common aneuploidy, please see Appendix.

Prenatal Genetic Screening and Testing of a Fetus
Discussion of prenatal genetic screening and testing in this Coverage Policy refers to sequencing-based noninvasive prenatal tests (NIPT) (i.e., cell-free deoxyribonucleic acid [DNA] screening) and invasive prenatal tests such as chorionic villus sampling [CVS] and amniocentesis. These tests are performed in early pregnancy and used to test for germline mutation genetic disorders.

Sequencing-Based Non-Invasive Prenatal Testing (NIPT)

Sequencing-based genomic testing, a type of NIPT has been proposed for use as an advanced screening test to assess whether a pregnant woman is at increased risk of having a fetus affected by a genetic disorder (American College of Obstetricians and Gynecologists [ACOG], 2016). One benefit of such screening is the potential decrease in the number of invasive procedures, and therefore, the decrease in the potential for miscarriage as a complication of invasive testing. As a screening test for genetic disorders, sequencing-based NIPT may also allow for reproductive options.

Sequencing-based testing evaluates short segments of relies on the presence of circulating fetal or cell-free deoxyribonucleic acid (DNA) in the maternal plasma during pregnancy. The clinical utility of sequencing-based NIPT has been established as a means to detect fetal trisomy 13, 18 and 22 in the published, peer-reviewed scientific literature for a woman at ≥ 10 weeks gestation with a viable, singleton pregnancy. No specific test has been established to be significantly different than the others for this purpose.

The sensitivity and specificity of cell-free DNA screening in a singleton gestation has been reported to be uniformly high, ranging from 99.1%-100% and 99.7%-100%, respectively, primarily for trisomy 21. Negative predictive values have been reported to be near, or at 100%, with positive predictive values of 83% and 55% for high- and average-risk populations, respectively. Laboratories variably report screening results as positive, negative or 'no call', a category to describe indeterminate or uninterpretable results. No-call results comprise approximately 4–8% of screened pregnancies and may occur secondary to assay failure, high assay variance or low fetal fraction. Low fetal fraction, defined as below 4%, confers significantly higher risk for fetal aneuploidy. Counseling before screening should include the possibility of results in this category (Dasche, 2016). Confirmatory CVS or amniocentesis is still needed in pregnancies with a positive result. According to the American College of Obstetricians and Gynecologists (2020), women with a positive screening test result should be counseled regarding their higher risk of aneuploidy and offered the option of diagnostic testing. Those who have a negative test result should be counseled regarding their lower adjusted and residual risk. Women with a negative screening result should not be offered additional screening tests for aneuploidy because this will increase their potential for a false-positive test result.

According to the American Congress of Obstetrics and Gynecologists (2020), cell free DNA screening can be performed in twin gestations. Sensitivity for trisomy 21 using cell free DNA for twin pregnancy is similar to singleton pregnancy although test failure may be higher. Because each fetus in a single pregnancy contribute different amounts of cell free DNA into the maternal circulation it is possible that an aneuploidy fetus would contribute less fetal DNA, masking the aneuploid test result. Nonetheless, noninvasive prenatal testing using cell-free DNA is considered an appropriate noninvasive prenatal screening option.

A number of sequencing-based NIPTs have been developed that utilize cell free DNA to detect fetal aneuploidy. Trisomies 13, 18 and 21 are detected with high accuracy. Many tests offer detection of one or more other syndromes, but detection of other aneuploidies has not have been determined to be clinically beneficial.

Luna Prenatal Test is a cell-based prenatal genetic test which isolates pure fetal DNA from rare fetal trophoblast cells circulating in maternal blood. This test in noninvasive, only requires a maternal blood sample and can be performed early in pregnancy, from 8 to 22 weeks of gestation. Currently, there is insufficient evidence in published, peer-reviewed scientific literature and lack of professional society to support this testing method.

Depending on the testing methodology used for each individual test, sequencing-based NIPTs may also detect various other fetal genetic disorders including: trisomy 7, 9, 16, 22 or other rare autosomal trisomies (RATs); sex-chromosome aneuploidy (e.g., Klinefelter syndrome, Turner syndrome, Jacob syndrome); vanishing twin syndrome; twin zygosity; fetal sex; microdeletions; single-gene disorders; and genetic cause of miscarriage. However, data are very limited in the published, peer-reviewed scientific literature regarding the predictive value of any of these tests to detect these additional fetal abnormalities, and whether maternal outcomes are improved if further invasive testing is required is unknown. Professional society support for these indications in the form of published consensus guidelines is also lacking.

The clinical utility of sequencing-based NIPT to detect trisomies 7, 9, 16 and 22 is also unknown; there is insufficient evidence in the published peer-reviewed scientific literature to establish whether pregnancy outcomes are improved by detection of these additional chromosomal abnormalities. Validation data regarding the predictive value of any NIPT to detect these trisomies are lacking in the published, peer-reviewed scientific literature.

Several laboratory methods allow for detection of microdeletions; however, data are lacking regarding the predictive value of NIPT for this indication and the impact on pregnancy outcomes is unknown. Such testing is not supported in the form of recommendations by ACMG (2013), the European Society of Human Genetics/American Society of Human Genetics and the Society for Maternal-Fetal Medicine. Validation data are limited regarding the role of NIPT for use as a screening tool in average-risk pregnancies or in a woman with a multiple gestation pregnancy and professional society support is lacking. At present, the role of NIPT for these indications has not been established. The clinical utility for NIPT to detect fetal sex is lacking in the scientific literature; professional society consensus guideline support is also lacking for this indication.

There are limited data in the published peer-reviewed scientific literature regarding the use of next generation sequencing performed via NIPT to identify single gene (monogenetic) disorders (Dan, et al., 2016; Verhoef, et al., 2016; Chitty, et al., 2015). However, unanswered questions about mosaicism and false positives raise concerns for harm and whether such testing requires confirmatory testing by invasive methods is not yet known (Jenkins, et al., 2017). The clinical utility of NIPT to identify single gene disorders is currently unknown given the limited published peer reviewed scientific evidence. Published professional society support in the form of consensus guidelines is also lacking.

Literature Review

Trisomies 13, 18, 21: The role of sequencing-based cell-free DNA testing to detect trisomy 13, 18 and 21 has been investigated in a number of prospective clinical trials, systematic reviews and technology assessments to determine if there are improved clinical outcomes as a result of such testing (Gil, et al., 2015; Zhang, et al., 2015; Norton, et al., 2012).

Zhang et al. (2015) reported results of the clinical performance of massively parallel sequencing-based NIPT in detecting trisomies 21, 18 and 13 in 147,314 clinical samples in low-risk and high-risk pregnancies in a prospective, multicenter observational study. Eligibility for NIPT included participants of at least 18 years old with a singleton or twin pregnancy at nine weeks' gestation or beyond. Individuals were considered high-risk for aneuploidy for any of the following: advanced maternal age (>35 years), a positive conventional Down syndrome screening test, abnormal sonographic markers, family history of aneuploidy or a previous pregnancy with a trisomic fetus. Individuals with none of the high-risk factors were defined as low risk for aneuploidy. NIPT performance in the detection of trisomy 21 in these two groups was compared using karyotyping or follow-up results as gold standard. There were a small number of cases positive for trisomies 18 and 13 in the low-risk group and NIPT performance for these two trisomies was not compared between risk groups. Results were obtained in 146,958 samples and outcome data were available

in 112,669 (76.7%). Repeat sampling was required in 3,213 cases; 145 had test failure. Overall sensitivity of NIPT was 99.17%, 98.24% and 100% for trisomies 21, 18 and 13, respectively. Specificity was 99.95%, 99.95% and 99.96% for trisomies 21, 18 and 13, respectively. There was no significant difference in test performance between high-risk and low-risk subjects (sensitivity, 99.21% vs 98.97% (p=0.82); specificity, 99.95% vs 99.95% (p=0.98)). Data suggest that sequencing-based NIPT to detect trisomy 21 has high sensitivity and specificity in high and low-risk populations.

Gil et al. (2015) updated results of a previously published meta-analysis to include 37 studies published up to January 4, 2015. The inclusion criteria were prospective and retrospective peer-reviewed studies reporting clinical validation or implementation of maternal cell-free DNA (cfDNA) testing in screening for aneuploidies, in which data on pregnancy outcome were provided for more than 85% of the study population. Twenty-four studies reported on the performance of screening by cfDNA analysis for trisomy 21. Pooled weighted DNA testing and detection rates (DR) 99.2% and 0.09%, respectively. Twenty-one studies reported on the performance of screening by cfDNA analysis for trisomy 18. Pooled weighted DR and FPR were 96.3% and 0.13%, respectively. A total of 18 studies reported on the performance of screening by cfDNA analysis for trisomy 13. Pooled weighted DR and FPR were 91.0% and 0.13%, respectively. The performance of cfDNA analysis of maternal blood in the identification of singleton pregnancies with trisomy 18 or 13, with respective DRs of 96% and 91%, and a combined FPR of 0.26%, is worse than is the performance of screening for trisomy 21. DR and FPR for monosomy X were 90.3% and 0.23%, respectively, and 93.0% and 0.14%, respective for sex chromosome aneuploidies other than monosomy X. For twin pregnancies, the DR for trisomy 21 was 93.7% and the FPR was 0.23. The authors note there are no advocates of screening for fetal trisomies 18 and 13 independently from screening for trisomy 21. Data from this systematic review and metaanalysis suggest a high detection rate and low false positive rate when testing for fetal trisomy 21.

There is sufficient evidence in the published, peer-reviewed scientific literature to establish the clinical validity of NIPT as a method to screen for these indications. Further, such testing is supported by published professional society consensus guidelines.

Norton et al. (2015) reported results of a prospective, multicenter trial comparing standard screening (i.e., measurement of nuchal translucency and biochemical analysis) and cell-free DNA (cfDNA) testing in pregnant women >18 years presenting for aneuploidy screening at 10-14 weeks of gestation. Study participants underwent both standard screening and cfDNA testing. Patients were ineligible if they were outside the gestational-age window, had no standard screening result, had known maternal aneuploidy or cancer, had conceived with the use of donor oocytes, or had a twin pregnancy or an empty gestational sac that was identified on ultrasonography. The primary outcome was the area under the receiver-operating-characteristic curve (AUC) for trisomy 21. The risk of trisomy 18 and 13 was also assessed. Lab personnel performing cfDNA analysis were blinded to all other clinical data, including results of ultrasonographic and standard screening. Using the maternal age of enrolled participants mid-trial, the estimate of the prevalence of trisomy 21 was adjusted to 1 in 500, and the required sample size reduced to 18,700. Of 18,955 women who were enrolled, results from 15,841 were available for analysis, with 1489 lost to follow-up.

Sixty-eight chromosomal abnormalities were identified (1 in 236 pregnancies). Of these, 38 were trisomy 21. The AUC for trisomy 21 was 0.999 for cfDNA testing and 0.958 for standard screening (p=0.001). Sensitivity to detect Trisomy 21 was 100% and 78.9% in the cfDNA and standard screening groups, respectively (p=0.008). False positive rates were 0.06% and 5.4% in the cfDNA and standard screening group, respectively (p<0.001). The positive predictive value for cfDNA testing was 80.9% compared with 3.4% for standard screening (P<0.001). Approximately 3% of cfDNA tests did not yield a result because of assay variation or a low fetal fraction.

Limitations noted by the authors include that the study only made a comparison between cfDNA testing and standard first-trimester screening and that the study was powered to compare only the detection of trisomy 21 in the two study groups. The authors also note the rate of detection for trisomy 21 using standard screening methods was lower than the 82%-87% seen in other studies.

Whether results of this test impacted clinical management or improved pregnancy outcomes is unknown. While cfDNA has been validated as a method to detect trisomy 21, maternal serum and nuchal translucency screening can identify the risk for a broad array of abnormalities that are not detectable on cfDNA testing. The role of this test in screening for aneuploidy in woman without increased risk remains uncertain; and clinical utility has not been established.

Sex-Chromosome Aneuploidy: Data are also limited in the published peer-reviewed scientific literature regarding the ability of NIPTs to detect sex-chromosome aneuploidies. In a validation study by Mazloom et al. (2013), massively parallel sequencing was performed on cfDNA isolated from the plasma of 1564 pregnant women with known fetal karyotype. Another study of 411 maternal samples from women with blinded-to-laboratory fetal karyotypes was then performed to determine the accuracy of the classification algorithm. The blinded validation yielded a detection rate of 96.2%, a false positive rate of 0.3% and a nonreportable rate of 5%. Although a high detection rate and low false positive rate was reported in this single study there is insufficient evidence to establish the effectiveness of NIPT to detect sex chromosome aneuploidy, and the impact of such results on treatment planning. Further, support for use of NIPT as a method to detect sex-chromosome aneuploidy is lacking in the form of professional society consensus guidelines. At this time the role of NIPT for this indication has not been established.

Microdeletions: Guidelines from the American College of Medical Genetics and Genomics (2013) and jointly published recommendations from the European Society of Human Genetics/American Society of Human Genetics (2015) as well as the Publications Committee of the Society for Maternal-Fetal Medicine (2015) note that use of NIPT to test for microdeletions is not recommended. Clinical validation studies relative to use of NIPTs to detect microdeletion syndromes are very limited in the published, peer-reviewed scientific literature. Wapner et al. (2015) reported on a test with a primary purpose of estimating the performance of a single-nucleotide polymorphism (SNP)-based noninvasive prenatal test for five microdeletion syndromes in 469 samples (358 plasma samples from pregnant women, 111 artificial plasma mixtures). These were amplified with the use of a massively multiplexed polymerase chain reaction, sequenced, and analyzed for the presence or absence of deletions of 22q11.2, 1p36, distal 5p, and the Prader-Willi/Angelman region. Detection rates were 97.8% for a 22q11.2 deletion, 100% for Prader-Willi, Angelman, 1p36 deletion, and cri-du-chat syndromes (24/24). False-positive rates were 0.76% for 22q11.2 deletion syndrome and 0.24% for cri-du-chat syndrome. No false positives occurred for Prader-Willi, Angelman or 1p36 deletion syndromes. SNP-based noninvasive prenatal microdeletion screening was accurate in this single study; however, additional validation studies are needed before such testing is useful in routine clinical practice.

Srinivasan et al. (2013) published results of a study involving 11 pregnant women. This small study was designed to determine the deep sequencing and analytic conditions needed to detect fetal subchromosome abnormalities across the genome from a maternal blood sample. Seven of seven cases of microdeletions, duplications, translocations, and one trisomy 20 were detected blindly by massively parallel sequencing. Small study numbers limit the ability to translate these results to routine clinical practice.

Professional Societies/Organizations

For a summary of professional society recommendations/guidelines regarding sequencing-based non-invasive prenatal testing, please see Appendix.

Invasive Prenatal Testing of a Fetus

Other prenatal genetic testing of a fetus for which clinical utility has been established includes testing when the results of testing will impact clinical decision-making and clinical outcome and the mother is a carrier of an X-linked condition, when both biologic parents are carriers of an autosomal recessively-inherited disorder or the mother is a known carrier of an autosomal recessively-inherited disorder and the father's status is unknown and unavailable and when one parent is the carrier of an autosomal dominantly–inherited disorder. Additionally, prenatal testing using targeted mutation analysis (CPT code 81220) for cystic fibrosis when fetal echogenic bowel has been identified on ultrasound is considered a standard of care based on professional society consensus guidelines. Prenatal reproductive comparative genomic hybridization (CGH) testing (chromosomal microarray analysis) (CPT code 81228, 81297) is also supported by guidelines published by ACOG (when a woman is undergoing invasive prenatal genetic testing or in the case of intrauterine fetal demise or stillbirth.

Literature Review

A number of prospective cohort and case series studies, systematic review and a meta-analysis have reported on the diagnostic accuracy for CGH/CMA compared with conventional karyotyping in greater than 13,000 prenatal samples (Dhillon, et al., 2014; Hillman, et al., 2013; Armengol, et al., 2012; Lee, et al., 2012; Reddy, et al., 2012; Shaffer, et al., 2012; Wapner, et al., 2012; Fiorentino, et al., 2011). Indications for testing include abnormal ultrasound, advanced maternal age, abnormal maternal serum screening, positive family history, parental anxiety and other or nonspecific. Overall, the data suggest microarray analysis provides significantly improved detection of clinically significant genomic abnormalities compared to those found with conventional karyotyping.

Professional Societies/Organizations

For a summary of professional society recommendations/guidelines (including Use Outside of the US) regarding invasive prenatal testing of a fetus, please click Appendix.

Germline Mutation Reproductive Genetic Testing for Recurrent Pregnancy Loss

Chromosomal analysis tests and cytogenetic testing: Published professional society consensus guidelines support the clinical usefulness of chromosomal analysis, such as karyotyping of peripheral blood and products of conception in the case of two or more pregnancy losses. There is also consensus support for molecular cytogenetic testing when karyotyping of the products of conception is not possible because of a lack of tissue sample or poor culture growth.

Microarray Analysis: Evidence in the published peer-reviewed scientific literature, including textbook and reproductive health society positions, evaluating the utility of microarray analysis such as CGH and SNP for recurrent pregnancy loss is lacking and strong evidence-based conclusions cannot be made regarding clinical utility, estimated recurrence rates, and impact on patient management and patient clinical outcomes.

In a recent systematic review and meta-analysis involving nine published studies comparing CMA testing on the products of conception with conventional karyotyping, Dhillon et al. (2014) reported that CMA testing resulted in a higher detection rate of abnormalities compared to karyotyping. The authors reported there was agreement between CMA and karyotyping in 86% of cases, CMA detected an additional 13% abnormalities versus karyotyping, and karyotyping detected 3% over CMA. The incidence of a variant of unknown significance was 2%. Unless uncertain findings were proven to be benign the authors included them as pathogenic. Overall, the authors acknowledged

"additional prospective research is needed in this area using a large cohort, with a representative, prospective population undergoing both a recognized reproducible array and karyotyping."

Testing for X-linked Recessive Traits: Genetic mutations such as X-linked recessive traits (e.g., highly skewed X-inactivation patterns) have also been investigated as a cause of RSA; however, data are limited. Some authors have reported that there is no correlation between skewed X-inactivation and RSA (Warburton, et al., 2009; Kaare, et al., 2008; Pasquier, et al., 2007; Hogge, et al., 2007). Moreover, recommendations of the National Society of Genetic Counselors (Laurino, et al., 2005) indicate that an association between X-inactivation patterns and pregnancy outcome has not been clearly established and further investigation should be conducted. Additionally, according to the ACOG practice bulletin (2001), commercially available testing for this and other related molecular genetic abnormalities is not widely available. At present, testing for highly skewed X-inactivation patterns as a cause of RSA is not well-supported in the literature.

Single Gene Mutation Analysis
Single gene mutation analysis is not indicated in the work-up of recurrent pregnancy loss. There is insufficient evidence in the published, peer-reviewed scientific literature to demonstrate clinical usefulness and it has not been established as a standard of care in clinical practice. To date, professional society support in the form of published consensus guidelines is lacking.

Genetic Testing for Other Gene Mutations (i.e., F7 [serum prothrombin conversion accelerator] gene mutation R353Q, F13B polypeptide gene mutation V34L, and PAI-1):
Genetic testing has been proposed for these gene variants; however, data are lacking regarding the clinical utility of these tests to inform health outcomes in an individual with an hereditary hypercoagulability disorder.

Literature Review
High quality controlled clinical trial data are lacking regarding the ability of genetic testing to inform improved health outcomes, including the prevention of venous thromboembolic events in individuals with F7 R353Q variant, F13B polypeptide V34L variant, and PAI-1.

Professional Societies/Organizations
For a summary of professional society recommendations/guidelines (including Use Outside of the US) regarding germline mutation reproductive genetic testing for recurrent pregnancy loss, please see Appendix.

<u>Germline Mutation Reproductive Genetic Testing for Infertility</u>
Infertility is defined as the failure to achieve pregnancy after 12 months of regular unprotected intercourse (Agency for Healthcare Research and Quality [AHRQ], 2008; American Society of Reproductive Medicine [ASRM], 2013). The etiology of infertility may have a genetic basis such as cystic fibrosis in a male with congenital bilateral absence of vas deferens, azoospermia or severe oligospermia. Genetic testing with targeted mutation analysis of the 23 CFTR mutations as described by the ACMG and ACOG is considered clinically useful. Karyotyping, Y-chromosome microdeletion testing in males with nonobstructive azoospermia or severe oligospermia, and sperm penetration assays may also be considered appropriate. According to the American Urological Association (Schlegel, et al., 2021a), detection of certain genetic causes of male infertility allows couples to be informed about the potential to transmit genetic abnormalities that may affect the health of offspring. Thus, an appropriate male evaluation may allow the couple to better understand the basis of their infertility and to obtain genetic counseling when appropriate.

The clinical utility of sperm DNA integrity testing has not been established in the published, peer-reviewed scientific literature. This test has been proposed to identify a male factor contributing to

unexplained infertility or in the treatment of infertility to direct interventions. Several tests for sperm DNA integrity are now available (e.g., Sperm Chromatin Structure Assay [SCSA], TUNEL assay, Comet assay). Another test to assess sperm DNA is the Sperm DNA Decondensation test (e.g., Human Sperm Activation Assay [HSAA], SDD™). The AUA (2011) reported that the assays demonstrate low sensitivity and high specificity; there is insufficient evidence to support the routine use of DNA integrity testing in the evaluation and management of male factor infertility.

Professional Societies/Organizations
For a summary of professional society/organization recommendations/guidelines regarding germline mutation reproductive genetic testing for infertility, please see Appendix.
Include what the comparators are and what the standard of care is
we need to understand what the alternative(s) are—what testing, treatment or device would or could be used instead? What is the gold standard/standard of care, and other approaches that may be considered,

Appendix

Professional Societies/Organizations Recommendations/Guidelines

Germline Carrier Testing for Familial Disease
American College of Medical Genetics and Genomics (ACMG): The ACMG (Gregg, et al., 2021) published a practice resource for screening of autosomal recessive and X-linked conditions during pregnancy and preconception recommending carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion. Their recommended approach to this involves a tiered system based on carrier frequency:

- Tier one includes the recommendations previously adopted by ACMG and ACOG adopting an ethic and population neutral approach when screening for cystic fibrosis and spinal muscular atrophy. It also includes additional carrier screening determined after risk assessment (i.e., personal medical history, family history, labs, and imaging).
- Tier two is based on an ACOG recommendation for conditions that have a severe or moderate phenotype and a carrier frequency of at least 1/100.
- Tier three is carrier screening for conditions with a carrier frequency ≥ 1/200.
- Tier four includes less common genes with no lower limit carrier screening frequency.

ACMG recommends all pregnant patients and those planning a pregnancy should be offered tier three carrier screening and not solely tier one and/or tier two as these do not provide equitable evaluation of all racial/ethnic groups.

In a policy statement regarding prenatal/preconception expanded carrier screening, ACMG (2013) notes:

- Disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction.
- The inclusion of disorders characterized by variable expressivity or incomplete penetrance and those known to be associated with a mild phenotype should be optional and made transparent when using these technologies for screening.
- For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed.

- The calculation of residual risk requires knowledge of two factors: one is the carrier frequency within a population, the other is the proportion of disease-causing alleles detected using the specific testing platform. Laboratories using multiplex platforms often have limited knowledge of one or both factors.
- There must be validated clinical association between the mutation(s) detected and the severity of the disorder.

In a policy statement regarding carrier screening for SMA (2008, reaffirmed 2013), ACMG notes:

- A negative screening test for one or both partners reduces but does not eliminate the possibility of an affected offspring, because the test sensitivity is <100% (~90% detection rate).
- Carrier testing should be offered to all couples regardless of race or ethnicity
- Carrier testing should be offered to asymptomatic individuals with a confirmed or suspected family history of SMA.
- A prerequisite for prenatal testing is the previous identification of the homozygous deletion in the proband or positive carrier status in the parents.

Regarding screening for Fragile X, ACMG notes (2004):

- Population carrier screening is not recommended at this time except as part of a well-defined clinical research protocol.
- DNA testing for permutation size alleles should be considered if a woman has ovarian failure before the age of 40, as part of the infertility evaluation and prior to in vitro fertilization.

The ACMG practice guidelines for carrier screening in individuals of Ashkenazi Jewish descent include the following recommendations regarding genetic testing (Gross, et al., 2008, reaffirmed 2013):

- Carrier screening should be offered to all individuals of Ashkenazi Jewish descent who are pregnant or considering pregnancy.
- Carrier screening for these disorders should include testing for the specific mutations related to the conditions, which will result in a carrier detection rate 95% for most disorders.
- The offering of such testing should ideally take place before pregnancy, thereby giving individuals time to make appropriate reproductive decisions based on their own personal choices and cultural backgrounds. Currently, the majority of testing takes place in the primary care obstetrical setting and not in the medical genetic specialty environment. However, regardless of the clinical setting, adequate counseling should be provided to anyone considering testing so that choices are informed.
- If only one member of a couple is of Ashkenazi Jewish background, then testing should still be offered with the individual of Ashkenazi Jewish descent being tested first

In a policy statement regarding laboratory standards and guidelines for population-based cystic fibrosis carrier screening, ACMG (2001) notes the following:

- CF carrier screening should be offered to all individuals regardless of ethnicity
- preconception testing be encouraged whenever possible, although testing will often occur in the prenatal setting
- Couple-based testing is recommended for Caucasian couples of Northern European and Ashkenazi Jewish descent, particularly when concurrently testing for other common genetic disorders in the latter population.

- a pan-ethnic mutation panel that includes all CF-causing mutations with an allele frequency of ≥0.1% in the general U.S. population is recommended.

ACMG (2011) states that an extended panel is not recommended for routine carrier screening of reproductive couples. The ACMG (2011) indications for CF genetic testing with the ACMG panel of 23 mutations include:

- carrier testing, partners of individuals with positive family history of CF
- carrier testing, partners of males with CBAVD
- carrier testing, general population of reproductive couples
- carrier testing, premarital population, to assist in selection of mate
- carrier testing, positive family history
- carrier testing, gamete donors
- preimplantation testing
- prenatal diagnostic testing, positive family history or for couples having a CF mutation in both partners
- prenatal diagnostic testing, echogenic bowel fetus during second trimester

American College of Obstetricians and Gynecologists (ACOG): A Committee Opinion on carrier screening for genetic conditions included the following recommendations (ACOG, 2017):

- General Recommendations
  - Information about genetic carrier screening should be provided to every pregnant woman. After counseling, a patient may decline any or all screening.
  - Carrier screening and counseling ideally should be performed before pregnancy.
  - If an individual is found to be a carrier for a specific condition, the individual's reproductive partner should be offered testing in order to receive informed genetic counseling about potential reproductive outcomes.
  - Concurrent screening of the patient and her partner is suggested if there are time constraints for decisions about prenatal diagnostic evaluation.
  - Carrier screening for a particular condition generally should be performed only once in a person's lifetime and the results should be documented in the patient's health record. Because of the rapid evolution of genetic testing, additional mutations may be included in newer screening panels. The decision to rescreen a patient should be undertaken only with the guidance of a genetics professional who can best assess the incremental benefit of repeat testing for additional mutations.
- Spinal Muscular Atrophy
  - Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant.
  - In patients with a family history of spinal muscular atrophy, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible before testing. If reports are not available, SMN1 deletion testing should be recommended for the low-risk partner
- Cystic Fibrosis
  - Carrier screening should be offered to all women who are considering pregnancy or are currently pregnant
  - Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening
  - If a woman's reproductive partner has cystic fibrosis or apparently isolated congenital bilateral absence of the vas deferens, the couple should be provided follow-up genetic counseling by an obstetrician–gynecologist or other health care provider with expertise in genetics for mutation analysis and consultation.
- Fragile X Syndrome

    - Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant.
    - If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation.
    - All identified individuals with intermediate results and carriers of a fragile X premutation or full mutation should be provided follow-up genetic counseling to discuss the risk to their offspring of inheriting an expanded full-mutation fragile X allele and to discuss fragile X-associated disorders (premature ovarian insufficiency and fragile X tremor/ataxia syndrome).
    - Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation.
    - DNA-based molecular analysis (e.g., Southern blot analysis and polymerase chain reaction) is the preferred method of diagnosis of fragile X syndrome and of determining FMR1 triplet repeat number (e.g., premutations). In rare cases, the size of the triplet repeat and the methylation status do not correlate, which makes it difficult to predict the clinical phenotype. In cases of this discordance, the patient should be referred to a genetics professional.
- Genetic Conditions in Individuals of Eastern and Central European Jewish Descent
    - When only one partner is of Ashkenazi Jewish descent, that individual should be offered screening first. If it is determined that this individual is a carrier, the other partner should be offered screening.
    - Tay–Sachs Disease
        - Screening for Tay–Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French–Canadian, or Cajun descent. Those with a family history consistent with Tay–Sachs disease also should be offered screening.
        - When one member of a couple is at high risk (i.e., of Ashkenazi Jewish, French–Canadian, or Cajun descent or has a family history consistent with Tay–Sachs disease) but the other partner is not, the high-risk partner should be offered screening. If the high-risk partner is found to be a carrier, the other partner also should be offered screening.
        - If Tay–Sachs disease screening is performed as part of pan-ethnic expanded carrier screening, it is important to recognize the limitations of the mutations screened in detecting carriers in the general population. In the presence of a family history of Tay–Sachs disease, expanded carrier screening panels are not the best approach to screening unless the familial mutation is included on the panel.
        - Referral to an obstetrician–gynecologist or other health care provider with genetics expertise may be helpful in instances of inconclusive enzyme testing results or in discussion of carrier testing of an individual with non-Ashkenazi Jewish ethnicity whose reproductive partner is a known carrier of Tay–Sachs disease.

Regarding expanded carrier screening, ACOG Committee Opinion (2017, reaffirmed 2020) notes the following:

- Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening.
- All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and

spinal muscular atrophy, as well as a complete blood count and screening for thalassemias and hemoglobinopathies.
- If a woman is found to be a carrier for a specific condition, her reproductive partner should be offered screening to provide accurate genetic counseling for the couple with regard to the risk of having an affected child.
- Individuals with a family history of a genetic disorder may benefit from the identification of the specific familial mutation or mutations rather than carrier screening.
- Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several of the following consensus-determined criteria: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life. Additionally, screened conditions should be able to be diagnosed prenatally and may afford opportunities for antenatal intervention to improve perinatal outcomes, changes to delivery management to optimize newborn and infant outcomes, and education of the parents about special care needs after birth.
- Carrier screening panels should not include conditions primarily associated with a disease of adult onset.

ACOG addresses hemoglobinopathies in pregnancy in Practice Bulletin No. 78 published in 2007. The updated Practice Advisory published in 2022 states, "Previous recommendations for hemoglobinopathy testing have used a race/ethnicity-based strategy. However, race and self-identified ethnicity are poor proxies for genetics since self-identification with a specific race/ethnicity may be incompatible with genetic ancestry. Given that approximately 1 in 66 people in the United States have a hemoglobinopathy trait, ACOG recommends offering universal hemoglobinopathy testing to persons planning pregnancy or at the initial prenatal visit if no prior testing results are available for interpretation. This helps ensure that at-risk individuals receive counseling about genetic risks; learn their reproductive options, which include preimplantation genetic testing and prenatal diagnosis; and make informed decisions. Hemoglobinopathy testing may be performed using hemoglobin electrophoresis or molecular genetic testing (eg, expanded carrier screening that includes sickle cell disease [SCD] and other hemoglobinopathies). The use of noninvasive prenatal diagnosis for SCD with cell-free fetal DNA is still experimental and currently not recommended."

Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists (CCMG): Clinical practice guidelines for carrier screening for thalassemia and hemoglobinopathies in Canada include the following recommendations (Langlois, et al., 2008):

- If both partners are found to be carriers of thalassemia or an Hb variant, or of a combination of thalassemia and a hemoglobin variant, they should be referred for genetic counselling- ideally prior to conception, or as early as possible in the pregnancy. Additional molecular studies may be required to clarify the carrier status of the parents and thus the risk to the fetus.
- Prenatal diagnosis should be offered to the pregnant woman/couple at risk for having a fetus affected with a clinically significant thalassemia or hemoglobinopathy.

The International Myotonic Dystrophy Consortium (IDMC, 2000): Published his society published genetic testing guidelines for DM1. Regarding reproductive carrier screening the Guidelines note that prenatal testing may be appropriate if:

- a parent has already been diagnosed with DM1, prenatal testing can be used to assess fetal risk

- a parent is at 50% risk and asymptomatic, the best approach is a two-step process by which the at-risk parent is tested first and prenatal testing done subsequently (if still necessary)

Preimplantation Genetic Testing of an Embryo
American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology (2007): Recommendations for preimplantation genetic diagnosis (PGD) include:

- Before PGD is performed, genetic counseling must be provided.
- PGD can reduce the risk for conceiving a child with a genetic abnormality carried by one or both parents if that abnormality can be identified with tests performed on a single cell.
- Prenatal diagnostic testing to confirm the results of PGD is encouraged strongly because PGD has technical limitations that include the possibility of false negatives.

Preimplantation Genetic Testing for Aneuploidy (PGT-A)
American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology (2007): Recommendations for PGD:

- Before PGD is performed, thorough education and counseling must be performed to ensure the patient understands the limitations of the technique, risk of error, and lack of evidence that PGD improves outcomes.
- Available evidence does not support the use of PGD as currently performed to improve live-birth rates in patients with advanced maternal age.
- Available evidence does not support the use of PGD as currently performed to improve live-birth rates in patients with previous implantation failure.
- Due to the high prevalence of aneuploidy in patients with recurrent implantation failure, decisions concerning future treatments should not be based on the results of PGD in one or more cycles.
- Available evidence does not support the use of PGD as currently performed to improve live-birth rates in patients with recurrent pregnancy loss.
- Available evidence does not support the use of PGD as currently performed to reduce miscarriage rates in patients with recurrent pregnancy loss related to aneuploidy.

Sequencing-Based Non-Invasive Prenatal Testing (NIPT)
American Congress of Obstetricians and Gynecologists (ACOG; 2020): Practice Bulletin 226 (2020, replaces Practice Bulletin 162) from ACOG includes the following information regarding screening for fetal chromosomal abnormalities:

- Screening and diagnostic testing for chromosomal abnormalities should be offered to all patients early in pregnancy regardless of maternal age or risk for chromosomal abnormality.
- Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies (trisomies 21, 13 and 18) and can be performed any time after 9-10 weeks gestation.
- If a patient chooses screening for aneuploidy only one screening approach should be used.
- Cell-free DNA screening can be performed in twin gestations.
- Sensitivity for trisomy 21 using cell free DNA for twin pregnancy is similar to singleton pregnancy although test failure may be higher.

In a Committee Opinion by ACOG/SMFM on microarrays and next-generation sequencing technologies (2016) the Committee notes that cell-free whole genome DNA screening is not recommended.

American College of Medical Genetics and Genomics ([ACMG], 2013): On behalf of the ACMG Gregg et al. published guidelines regarding noninvasive prenatal screening for aneuploidy. The Guidelines note:

- NIPS is not able to distinguish specific forms of aneuploidy. Identification of the mechanism of aneuploidy is important for recurrence risk counseling and emphasizes the importance of diagnostic testing following NIPS.
- NIPS does not screen for single-gene mutations.
- Uninformative test results due to insufficient isolation of cell-free fetal DNA could lead to a delay in diagnosis or eliminate the availability of information for risk assessment.
- NIPS does not screen for open neural tube defects.
- NIPS does not replace the utility of a first-trimester ultrasound examination
- Limited data are currently available on the use of NIPS in twins and higher-order pregnancies.
- NIPS has no role in predicting late-pregnancy complications.

European Society of Human Genetics (ESHG) and the American Society of Human Genetics (ASHG): On behalf of the ESHG/ASHG, Dondorp et al. (2015) published recommendations regarding NIPTs. The recommendations note the following:

- NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFTS. However, a positive NIPT result should not be regarded as a final diagnosis
- Expanding NIPT-based prenatal screening to also report on sex chromosomal abnormalities and microdeletions not only raises ethical concerns related to information and counseling challenges but also risks reversing the important reduction in invasive testing achieved with implementation of NIPT for aneuploidy, and is therefore currently not recommended.

Society for Maternal-Fetal Medicine Publications Committee (2015): In publication #36 the Committee notes the following:

- The presence of a second gestational sac has been associated with false-positive cfDNA results; therefore, this test is not a good option for women with a "vanishing twin" or empty second sac. At this time, the data are too limited to recommend routine cfDNA aneuploidy screening in women with multifetal gestations.
- It is important for providers to recognize that a positive result for any of these aneuploidies confers a chance that the fetus is affected, which is usually far <99%, particularly in lower risk patients.
- When testing for rare conditions (such as aneuploidy in younger women), the positive predictive value is much lower than when testing for more common conditions (such as trisomy 21 in older women). More false-positive results are expected in women who are at low risk or when screening is done for very rare conditions. The PPV for trisomy 21 has been reported as varying from 45% in low-risk patients to ≥96% in the highest risk patients. In one study of diagnostic testing after abnormal cfDNA screens, aneuploidy was confirmed in 93% of trisomy 21 cases, in 64% of trisomy 18 cases, in 44% of trisomy 13 cases, and in 38% of sex chromosomal abnormalities.
- Testing for microdeletions using free cell DNA has not been validated in clinical trials; rather, proof-of-principle studies have included the mixing of normal and abnormal DNA in laboratory samples at ratios thought to represent typical fetal fraction. Even with very high sensitivity and specificity, at such low prevalence, the PPV of such testing is likely very low, and the clinical utility is unclear. At this time, routine screening for microdeletions with cfDNA is not recommended.

Invasive Prenatal Testing of a Fetus

American Congress of Obstetricians and Gynecologists (ACOG)/Maternal and the Society for Maternal-Fetal Medicine (SMFM): In an update of the 2013 committee opinion, ACOG/SMFM published a document regarding the use of chromosomal microarray analysis in prenatal diagnosis (2016). ACOG made the following recommendations:

- In patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis, chromosomal microarray analysis is recommended. This test replaces the need for fetal karyotype.
- In patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.
- Most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age; therefore, the use of this test for prenatal diagnosis can be considered for all women, regardless of age.
- In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (i.e., amniotic fluid, placenta, or products of conception) is recommended because of its increased likelihood of obtaining results and improved detection of causative abnormalities.
- Limited data are available on the clinical utility of chromosomal microarray analysis to evaluate first-trimester and second-trimester pregnancy losses; therefore, this is not recommended at this time.
- Comprehensive patient pretest and posttest genetic counseling from qualified personnel such as a genetic counselor or geneticist regarding the benefits, limitations, and results of chromosomal microarray analysis is essential.

Germline Mutation Reproductive Genetic Testing for Recurrent Pregnancy Loss

American College of Medical Genetics and Genomics (ACMG, 2013): On behalf of the ACMG, Hickey et al. published guidelines regarding MTHFR polymorphism testing. The guideline notes that MTHFR polymorphism genotyping should not be ordered as part of the clinical evaluation for thrombophilia or recurrent pregnancy loss.

American Congress of Obstetricians and Gynecologists ([ACOG]: A Practice Bulletin regarding thromboembolism in pregnancy (ACOG, 2016) notes women who have a history of thrombosis who have not had a complete evaluation of underlying etiologies should be tested for antiphospholipid antibodies and inherited thrombophilias.

A Practice Bulletin regarding inherited thrombophilias in pregnancy (ACOG, 2018) notes:

- Screening for inherited thrombophilias is useful only when results will impact management decisions. It is not useful when treatment is indicated for other risk factors.
- Screening is not recommended for women with a history of fetal loss or adverse pregnancy outcomes (e.g., abruption, preeclampsia, fetal growth restriction).
- Screening with MTHFR mutation analysis or fasting homocysteine level is not recommended.

ACOG/The Society for Maternal Fetal Medicine: ACOG/SMFM (2016) published a Committee Opinion regarding chromosomal microarray (CMA) and next generation sequencing for prenatal diagnosis. The Committee notes that CMA of fetal tissue (i.e., amniotic fluid, placenta, products of conception) is recommended in the evaluation of intrauterine death or stillbirth when further cytogenetic analysis is desired. The Opinion also noted that whole exome and whole genome sequencing for prenatal diagnosis is not recommended outside the context of clinical trials. Cell-free DNA screening is not recommended.

American Society of Reproductive Medicine ([ASRM], 2012): ASRM published the following recommendations for the evaluation and treatment of recurrent pregnancy loss:

- assessment of RSA focuses on screening for genetic factors and antiphospholipid syndrome, assessment of uterine anomaly, hormonal and metabolic factors, and lifestyle variables. These may include the following genetic tests:

    - peripheral karyotypic analysis of parents
    - karyotypic analysis of products of conception in the setting of ongoing therapy for RSA

ASRM notes if a remediable cause of recurrent pregnancy loss is identified cytogenetic analysis of subsequent losses can be employed to determine whether the event was random and not a treatment failure per se. If a 46 XX karyotype is revealed by cytogenetic analysis, reflex DNA extraction and analysis of maternal serum by microsatellite analysis may permit differentiation between a fetal source versus a maternal source.

National Society for Genetic Counselors ([NSGC], 2005, reaffirmed 2010): on behalf of the NSGC, Laurino, et al. published guidelines noting a referral to a genetics specialist is indicated when prior evaluations for RSA have been normal and when the pregnancy, medical and family history evaluation indicate a possible genetic cause for RSA. Other NSGC genetic evaluation and testing recommendations include the following:

- when possible, chromosomal analysis on fetal tissue
- routine karyotyping of each partner
- testing for factor V Leiden and prothrombin G20210A should be considered
- testing for less common thrombophilias (anticoagulant protein C, protein S, antithrombin III) should be reserved for those women with a personal and/or family history of venous thromboembolism
- testing for thermolabile C677T methylenetetrahydrofolate reductase mutation (MTHFR) is not justified (associated with some hereditary thrombophilia patterns such as hyperhomocysteinemia)
- testing for alpha thalassemia for Southeast Asian and Mediterranean ancestry is recommended (with or without a personal family history of fetal hydrops)
- specialized chromosomal studies such as comparative genome hybridization, subtelomeric studies, interphase studies on sperm, and assays for skewed X-inactivation patterns are not warranted (the clinical utility has yet to be proven)

The NSGC reaffirmed that the use of specialized chromosomal studies such as comparative genome hybridization, subtelomeric studies, interphase studies on sperm and assays for skewed X-inactivation patterns are not warranted at this time, as their clinical utility has yet to be determined.

Pregnancy and Thrombosis Working Group: On behalf of this association, Duhl et al. (2007) published a consensus report and recommendations for prevention and treatment of VTE and adverse pregnancy outcome. The authors acknowledged that no clear conclusions can be drawn from the studies they reviewed regarding an association between inherited thrombophilias and adverse pregnancy outcomes-some studies show a positive relationship, and other studies show no relationship. According to Duhl, most of the research demonstrated that FVL is not typically associated with pregnancy loss prior to 10 weeks' gestation. More evidence exists suggesting that a loss after 10 weeks' gestation may be associated with these disorders.

Germline Mutation Reproductive Genetic Testing for Infertility

American Society of Reproductive Medicine (ASRM; 2013): The Practice Committee of the ASRM (2013) noted there is insufficient evidence to recommend the routine use of sperm DNA integrity tests in the evaluation and treatment of the infertile couple.

American Urological Association (AUA) (Schlegel, et al., 2021): Regarding guidelines statements directed to genetic testing for male infertility, the AUA notes:

- Karyotype and Y-chromosome microdeletion analysis should be recommended for men with primary infertility and azoospermia or severe oligozoospermia (<5 million sperm/mL) with elevated FSH or testicular atrophy or a presumed diagnosis of impaired sperm production as the cause of azoospermia. (Expert Opinion)

- Clinicians should recommend Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutation carrier testing (including assessment of the 5T allele) in men with vasal agenesis or idiopathic obstructive azoospermia. (Expert Opinion)

- Sperm DNA fragmentation analysis is not recommended in the initial evaluation of the infertile couple. (Moderate Recommendation; Evidence Level Grade: C)

- For couples with recurrent pregnancy loss, men should be evaluated with karyotype (Expert Opinion) and sperm DNA fragmentation. (Moderate Recommendation; Evidence Level Grade: C)

Body of evidence strength Grade C in support of a Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence is likely to change confidence.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	A58917 Billing and Coding: Molecular Pathology and Genetic Testing	10/23/2023
LCD	National Government Services,Inc	Molecular Pathology Procedures (L35000) 7/1/2020	8/6/2023
	First Coast Service Options, Inc.	Molecular Pathology Procedures (L34519) 12/12/2021	12/12/2021

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Genetic Counseling

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family

HCPCS Codes	Description
S0265	Genetic counseling, under physician supervision, each 15 minutes

Germline Carrier Testing for Familial Disease

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81234	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81239	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

CPT®* Codes	Description
81244	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease) gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, 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) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81271	HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81274	HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant

CPT®* Codes	Description
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81330	SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81400†	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401††	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81403††	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons
81408	Molecular pathology procedure, Level 9 (eg, analysis of > 50 exons in a single gene by DNA sequence analysis)
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at

CPT®* Codes	Description
	least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
81479†††	Unlisted molecular pathology procedure
83080	b-Hexosaminidase, each assay

†**Note: Considered Not Medically Necessary when used to report:**

- **F7 (coagulation factor VII [serum prothrombin conversion accelerator] R353Q variant) for recurrent pregnancy loss (81400)**
- **F13B (coagulation factor XIII, B polypeptide, V34L variant) for recurrent pregnancy loss (81400)**

††**Note: Considered Experimental/Investigational/Unproven when used to report:**

- **APOE (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4) (81401)**
- **molecular testing for highly skewed X-inactivation patterns for recurrent pregnancy loss (81401)**
- **RHD (Rh blood group, D antigen) (eg, hemolytic disease of the fetus and newborn, Rh maternal/fetal compatibility), deletion analysis (eg, exons 4, 5, and 7, pseudogene), performed on cell-free fetal DNA in maternal blood (81403)**

†††**Note: Considered Medically Necessary when used to report any covered genetic test for germline mutation carrier testing for familial disease that does not have an assigned CPT/HCPCS code when criteria in the applicable policy statements listed above are met**

HCPCS Codes	Description
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for Von Hippel-Lindau disease
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin E beta-thalassemia
S3849	Genetic testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3853	Genetic testing for myotonic muscular dystrophy

Considered Medically Necessary when performed for preconception or prenatal carrier testing for a biologic parent of Ashkenazi Jewish descent:

CPT®* Codes	Description
81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1

ICD-10-CM Diagnosis Codes	Description
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.438	Encounter for other genetic testing of female for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management
Z31.448	Encounter for other genetic testing of male for procreative management
Z3A.01-Z3A.49	Weeks of gestation

Not Covered or Reimbursable:

ICD-10-CM Diagnosis Codes	Description
	All other diagnosis codes

Not Covered or Reimbursable:

CPT®* Codes	Description
81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions
0400U	Obstetrics (expanded carrier screening), 145 genes by next-generation sequencing, fragment analysis and multiplex ligation-dependent probe amplification, DNA, reported as carrier positive or negative

Preimplantation Genetic Testing of an Embryo

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81234	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
81239	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease) gene analysis; common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant

CPT®* Codes	Description
81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
81271	HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81274	HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett Syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
81330	SMPD1 (sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81400†	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401††	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81403††	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

CPT®* Codes	Description
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons
81408	Molecular pathology procedure, Level 9 (eg, analysis of > 50 exons in a single gene by DNA sequence analysis)
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
81479†††	Unlisted molecular pathology procedure
83080	b-Hexosaminidase, each assay
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos
89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos
0396U	Obstetrics (pre-implantation genetic testing), evaluation of 300000 DNA single-nucleotide polymorphisms (SNPs) by microarray, embryonic tissue, algorithm reported as a probability for single-gene germline conditions

†Note: Considered Not Medically Necessary when used to report:

- **F7 (coagulation factor VII [serum prothrombin conversion accelerator] R353Q variant) for recurrent pregnancy loss (81400)**
- **F13B (coagulation factor XIII, B polypeptide, V34L variant) for recurrent pregnancy loss (81400)**

††Note: Considered Experimental/Investigational/Unproven when used to report:

- **APOE (apolipoprotein E) (eg, hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (eg, *2, *3, *4) (81401)**
- **molecular testing for highly skewed X-inactivation patterns for recurrent pregnancy loss (81401)**
- **RHD (Rh blood group, D antigen) (eg, hemolytic disease of the fetus and newborn, Rh maternal/fetal compatibility), deletion analysis (eg, exons 4, 5, and 7, pseudogene), performed on cell-free fetal DNA in maternal blood (81403)**

†††Note: Considered Medically Necessary when used to report any covered genetic test for preimplantation diagnostic testing of an embryo that does not have an assigned CPT/HCPCS code when criteria in the applicable policy statements listed above are met
Considered Experimental/Investigational/Unproven when used to report:

- **CHEK2 genetic testing with full sequence analysis or deletion/duplication analysis SDHAF2 gene testing**
- **PALB2 deletion/duplication analysis**
- **FANCA gene mutation testing**

HCPCS Codes	Description
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for Von Hippel-Lindau disease
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness
S3845	Genetic testing for alpha-thalassemia
S3846	Genetic testing for hemoglobin E beta-thalassemia
S3849	Genetic testing for Niemann-Pick disease
S3850	Genetic testing for sickle cell anemia
S3853	Genetic testing for myotonic muscular dystrophy

Considered Not Medically Necessary:

CPT®* Codes	Description
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions

Not Covered or Reimbursable:

CPT®* Codes	Description
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 (eg, parent)

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (ie, detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (ie, detection of large gene rearrangements)
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
81266	Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)

CPT®* Codes	Description
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81370	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1

CPT®* Codes	Description
81371	HLA Class I and II typing, low resolution (eg, antigen equivalents); HLA-A, -B, and –DRB1 (eg, verification typing)
81372	HLA Class I typing, low resolution (eg, antigen equivalents); complete (ie, HLA-A, -B, and -C)
81373	HLA Class I typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-A, -B, or -C), each
81374	HLA Class I typing, low resolution (eg, antigen equivalents); one antigen equivalent (eg, B*27), each
81375	HLA Class II typing, low resolution (eg, antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
81376	HLA Class II typing, low resolution (eg, antigen equivalents); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81377	HLA Class II typing, low resolution (eg, antigen equivalents); one antigen equivalent, each
81378	HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and -DRB1
81379	HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and -C)
81380	HLA Class I typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-A, -B, or -C), each
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, B*57:01P), each
81382	HLA Class II typing, high resolution (ie, alleles or allele groups); one locus (eg, HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81383	HLA Class II typing, high resolution (ie, alleles or allele groups); one allele or allele group (eg, HLA-DQB1*06:02P), each
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis);

CPT®* Codes	Description
	duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
81437	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
81438	Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL

HCPCS Codes	Description
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

Preimplantation Genetic Testing for Aneuploidy (PGT-A)

Considered Not Medically Necessary:

CPT®* Codes	Description
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells

Sequencing-Based Non-Invasive Prenatal Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met except when used to report not covered or reimbursable microdeletion testing:

CPT®* Codes	Description
81420	Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21

CPT®* Codes	Description
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
0327U	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed

ICD-10-CM Diagnosis Codes	Description
O09.00-O09.03	Supervision of pregnancy with history of infertility
O09.10-O09.13	Supervision of pregnancy with history of ectopic pregnancy,
O09.A0-O09.A3	Supervision of pregnancy with history of molar pregnancy
O09.211-O09.219	Supervision of pregnancy with history of pre-term labor
O09.291-O09.299	Supervision of pregnancy with other poor reproductive or obstetric history
O09.30-O09.33	Supervision of pregnancy with insufficient antenatal care
O09.40-O09.43	Supervision of pregnancy with grand multiparity
O09.511-O09.519	Supervision of elderly primigravida
O09.521-O09.529	Supervision of elderly multigravida
O09.611-O09.619	Supervision of young primigravida
O09.621-O09.629	Supervision of young multigravida
O09.70-O09.73	Supervision of high risk pregnancy due to social problems
O09.811-O09.819	Supervision of pregnancy resulting from assisted reproductive technology
O09.821-O09.829	Supervision of pregnancy with history of in utero procedure during previous pregnancy
O09.891-O09.899	Supervision of other high risk pregnancies
O09.90-O09.93	Supervision of high risk pregnancy, unspecified
O10.011-O10.019	Pre-existing essential hypertension complicating pregnancy
O10.111-O10.119	Pre-existing hypertensive heart disease complicating pregnancy
O10.211-O10.219	Pre-existing hypertensive chronic kidney disease complicating pregnancy
O10.311-O10.319	Pre-existing hypertensive heart and chronic kidney disease complicating pregnancy

ICD-10-CM Diagnosis Codes	Description
O10.411-O10.419	Pre-existing secondary hypertension complicating pregnancy
O10.911-O10.919	Unspecified pre-existing hypertension complicating pregnancy
O11.1-O11.9	Pre-existing hypertension with pre-eclampsia
O12.00-O12.03	Gestational edema
O12.10-O12.13	Gestational proteinuria
O12.20-O12.23	Gestational edema with proteinuria
O13.1-O13.9	Gestational [pregnancy-induced] hypertension without significant proteinuria
O14.00	Mild to moderate pre-eclampsia, unspecified trimester
O14.02	Mild to moderate pre-eclampsia, second trimester
O14.03	Mild to moderate pre-eclampsia, third trimester
O14.10	Mild to moderate pre-eclampsia, unspecified trimester
O14.12	Severe pre-eclampsia, second trimester
O14.13	Severe pre-eclampsia, third trimester
O14.20	HELLP syndrome (HELLP), unspecified trimester
O14.22	HELLP syndrome (HELLP), second trimester
O14.23	HELLP syndrome (HELLP), third trimester
O14.90	Unspecified pre-eclampsia, unspecified trimester
O14.92	Unspecified pre-eclampsia, second trimester
O14.93	Unspecified pre-eclampsia, third trimester
O15.00	Eclampsia complicating pregnancy, unspecified trimester
O15.02	Eclampsia complicating pregnancy, second trimester
O15.03	Eclampsia complicating pregnancy, third trimester
O16.1	Unspecified maternal hypertension, first trimester
O16.2	Unspecified maternal hypertension, second trimester
O16.3	Unspecified maternal hypertension, third trimester
O16.9	Unspecified maternal hypertension, unspecified trimester
O21.0-O21.9	Excessive vomiting in pregnancy
O22.00-O22.03	Varicose veins of lower extremity in pregnancy
O22.10-O22.13	Genital varices in pregnancy
O22.20-O22.23	Superficial thrombophlebitis in pregnancy
O22.30-O22.33	Deep phlebothrombosis in pregnancy
O22.40-O22.43	Hemorrhoids in pregnancy
O22.50-O22.53	Cerebral venous thrombosis in pregnancy

ICD-10-CM Diagnosis Codes	Description
O22.8X1-O22.8X9	Other venous complications in pregnancy
O22.90-O22.93	Venous complication in pregnancy, unspecified
O23.00-O23.03	Infections of kidney in pregnancy
O23.10-O23.13	Infections of bladder in pregnancy
O23.20-O23.23	Infections of urethra in pregnancy
O23.30-O23.33	Infections of other parts of urinary tract in pregnancy
O23.40-O23.43	Unspecified infection of urinary tract in pregnancy
O23.511-O23.519	Infections of cervix in pregnancy
O23.521-O23.529	Salpingo-oophoritis in pregnancy
O23.591-O23.599	Infection of other part of genital tract in pregnancy
O23.90-O23.93	Unspecified genitourinary tract infection in pregnancy
O24.011-O24.019	Pre-existing diabetes mellitus, type 1, in pregnancy
O24.111-O24.119	Pre-existing diabetes mellitus, type 2, in pregnancy
O24.311-O24.319	Unspecified pre-existing diabetes mellitus in pregnancy
O24.410-O24.419	Gestational diabetes mellitus in pregnancy
O24.811-O24.819	Other pre-existing diabetes mellitus in pregnancy
O24.911-O24.919	Unspecified diabetes mellitus in pregnancy
O25.10-O25.13	Malnutrition in pregnancy
O26.00-O26.03	Excessive weight gain in pregnancy
O26.10-O26.13	Low weight gain in pregnancy
O26.20-O26.23	Pregnancy care for patient with recurrent pregnancy loss
O26.30-O26.33	Retained intrauterine contraceptive device in pregnancy
O26.40-O26.43	Herpes gestationis
O26.50-O26.53	Maternal hypotension syndrome

ICD-10-CM Diagnosis Codes	Description
O26.611-O26.619	Liver and biliary tract disorders in pregnancy
O26.711-O26.719	Subluxation of symphysis (pubis) in pregnancy
O26.821-O26.829	Pregnancy related peripheral neuritis
O26.831-O26.839	Pregnancy related renal disease
O26.841-O26.849	Uterine size-date discrepancy
O26.851-O26.859	Spotting complicating pregnancy
O26.891-O26.899	Other specified pregnancy related conditions
O26.90-O26.93	Pregnancy related conditions, unspecified
O28.0-O28.9	Abnormal findings on antenatal screening of mother
O30.001-O30.009	Twin pregnancy, unspecified number of placenta and unspecified number of amniotic sacs
O30.011-O30.019	Twin pregnancy, monochorionic/monoamniotic
O30.021-O30.029	Conjoined twin pregnancy
O30.031-O30.039	Twin pregnancy, monochorionic/diamniotic
O30.041-O30.049	Twin pregnancy, dichorionic/diamniotic
O30.091-O30.099	Twin pregnancy, unable to determine number of placenta and number of amniotic sacs
O30.90-O30.93	Multiple gestation, unspecified
O31.00X0	Papyraceous fetus, unspecified trimester, not applicable or unspecified
O31.00X1	Papyraceous fetus, unspecified trimester, fetus 1
O31.00X2	Papyraceous fetus, unspecified trimester, fetus 2
O31.01X0	Papyraceous fetus, first trimester, not applicable or unspecified
O31.01X1	Papyraceous fetus, first trimester, fetus 1
O31.01X2	Papyraceous fetus, first trimester, fetus 2
O31.02X0	Papyraceous fetus, second trimester, not applicable or unspecified
O31.02X1	Papyraceous fetus, second trimester, fetus 1
O31.02X2	Papyraceous fetus, second trimester, fetus 2
O31.03X0	Papyraceous fetus, third trimester, not applicable or unspecified
O31.03X1	Papyraceous fetus, third trimester, fetus 1
O31.03X2	Papyraceous fetus, third trimester, fetus 2
O31.10X0	Continuing pregnancy after spontaneous abortion of one fetus or more, unspecified trimester, not applicable or unspecified
O31.10X1	Continuing pregnancy after spontaneous abortion of one fetus or more, unspecified trimester, fetus 1

ICD-10-CM Diagnosis Codes	Description
O31.10X2	Continuing pregnancy after spontaneous abortion of one fetus or more, unspecified trimester, fetus 2
O31.11X0	Continuing pregnancy after spontaneous abortion of one fetus or more, first trimester, not applicable or unspecified
O31.11X1	Continuing pregnancy after spontaneous abortion of one fetus or more, first trimester, fetus 1
O31.11X2	Continuing pregnancy after spontaneous abortion of one fetus or more, first trimester, fetus 2
O31.12X0	Continuing pregnancy after spontaneous abortion of one fetus or more, second trimester, not applicable or unspecified
O31.12X1	Continuing pregnancy after spontaneous abortion of one fetus or more, second trimester, fetus 1
O31.12X2	Continuing pregnancy after spontaneous abortion of one fetus or more, second trimester, fetus 2
O31.13X0	Continuing pregnancy after spontaneous abortion of one fetus or more, third trimester, not applicable or unspecified
O31.13X1	Continuing pregnancy after spontaneous abortion of one fetus or more, third trimester, fetus 1
O31.13X2	Continuing pregnancy after spontaneous abortion of one fetus or more, third trimester, fetus 2
O31.20X0	Continuing pregnancy after intrauterine death of one fetus or more, unspecified trimester, not applicable or unspecified
O31.20X1	Continuing pregnancy after intrauterine death of one fetus or more, unspecified trimester, fetus 1
O31.20X2	Continuing pregnancy after intrauterine death of one fetus or more, unspecified trimester, fetus 2
O31.21X0	Continuing pregnancy after intrauterine death of one fetus or more, first trimester, not applicable or unspecified
O31.21X1	Continuing pregnancy after intrauterine death of one fetus or more, first trimester, fetus 1
O31.21X2	Continuing pregnancy after intrauterine death of one fetus or more, first trimester, fetus 2
O31.22X0	Continuing pregnancy after intrauterine death of one fetus or more, second trimester, not applicable or unspecified
O31.22X1	Continuing pregnancy after intrauterine death of one fetus or more, second trimester, fetus 1
O31.22X2	Continuing pregnancy after intrauterine death of one fetus or more, second trimester, fetus 2
O31.23X0	Continuing pregnancy after intrauterine death of one fetus or more, third trimester, not applicable or unspecified
O31.23X1	Continuing pregnancy after intrauterine death of one fetus or more, third trimester, fetus 1
O31.23X2	Continuing pregnancy after intrauterine death of one fetus or more, third trimester, fetus 2
O31.30X0	Continuing pregnancy after elective fetal reduction of one fetus or more, unspecified trimester, not applicable or unspecified
O31.30X1	Continuing pregnancy after elective fetal reduction of one fetus or more, unspecified trimester, fetus 1

ICD-10-CM Diagnosis Codes	Description
O31.30X2	Continuing pregnancy after elective fetal reduction of one fetus or more, unspecified trimester, fetus 2
O31.31X0	Continuing pregnancy after elective fetal reduction of one fetus or more, first trimester, not applicable or unspecified
O31.31X1	Continuing pregnancy after elective fetal reduction of one fetus or more, first trimester, fetus 1
O31.31X2	Continuing pregnancy after elective fetal reduction of one fetus or more, first trimester, fetus 2
O31.32X0	Continuing pregnancy after elective fetal reduction of one fetus or more, second trimester, not applicable or unspecified
O31.32X1	Continuing pregnancy after elective fetal reduction of one fetus or more, second trimester, fetus 1
O31.32X2	Continuing pregnancy after elective fetal reduction of one fetus or more, second trimester, fetus 2
O31.33X0	Continuing pregnancy after elective fetal reduction of one fetus or more, third trimester, not applicable or unspecified
O31.33X1	Continuing pregnancy after elective fetal reduction of one fetus or more, third trimester, fetus 1
O31.33X2	Continuing pregnancy after elective fetal reduction of one fetus or more, third trimester, fetus 2
O31.8X10	Other complications specific to multiple gestation, first trimester, not applicable or unspecified
O31.8X11	Other complications specific to multiple gestation, first trimester, fetus 1
O31.8X12	Other complications specific to multiple gestation, first trimester, fetus 2
O31.8X20	Other complications specific to multiple gestation, second trimester, not applicable or unspecified
O31.8X21	Other complications specific to multiple gestation, second trimester, fetus 1
O31.8X22	Other complications specific to multiple gestation, second trimester, fetus 2
O31.8X30	Other complications specific to multiple gestation, third trimester, not applicable or unspecified
O31.8X31	Other complications specific to multiple gestation, third trimester, fetus 1
O31.8X32	Other complications specific to multiple gestation, third trimester, fetus 2
O31.8X90	Other complications specific to multiple gestation, unspecified trimester, not applicable or unspecified
O31.8X91	Other complications specific to multiple gestation, unspecified trimester, fetus 1
O31.8X92	Other complications specific to multiple gestation, unspecified trimester, fetus 2
O34.00-O34.03	Maternal care for unspecified congenital malformation of uterus
O34.10-O34.13	Maternal care for benign tumor of corpus uteri
O34.211-O34.29	Maternal care due to uterine scar from previous cesarean delivery
O34.30-O34.33	Maternal care for cervical incompetence
O34.40-O34.43	Maternal care for other abnormalities of cervix
O34.511-O34.519	Maternal care for incarceration of gravid uterus

ICD-10-CM Diagnosis Codes	Description
O34.521-O34.529	Maternal care for prolapse of gravid uterus
O34.531-O34.539	Maternal care for retroversion of gravid uterus
O34.591-O34.599	Maternal care for other abnormalities of gravid uterus
O34.60-O34.63	Maternal care for abnormality of vagina
O34.70-O34.73	Maternal care for abnormality of vulva and perineum
O34.80-O34.83	Maternal care for other abnormalities of pelvic organs
O34.90-O34.93	Maternal care for abnormality of pelvic organ, unspecified
O35.0XX0	Maternal care for (suspected) central nervous system malformation in fetus, not applicable or unspecified (Code invalid 09/30/2022)
O35.0XX1	Maternal care for (suspected) central nervous system malformation in fetus, fetus 1 (Code invalid 09/30/2022)
O35.0XX2	Maternal care for (suspected) central nervous system malformation in fetus, fetus 2 (Code invalid 09/30/2022)
O35.00X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, not applicable or unspecified
O35.00X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, fetus 1
O35.00X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, unspecified, fetus 2
O35.01X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, not applicable or unspecified
O35.01X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, fetus 1
O35.01X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, agenesis of the corpus callosum, fetus 2
O35.02X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, not applicable or unspecified
O35.02X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 1
O35.02X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, anencephaly, fetus 2
O35.03X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, not applicable or unspecified
O35.03X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, fetus 1
O35.03X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, choroid plexus cysts, fetus 2
O35.04X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, not applicable or unspecified
O35.04X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, fetus 1

ICD-10-CM Diagnosis Codes	Description
O35.04X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, encephalocele, fetus 2
O35.05X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, not applicable or unspecified
O35.05X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, fetus 1
O35.05X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, holoprosencephaly, fetus 2
O35.06X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, not applicable or unspecified
O35.06X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, fetus 1
O35.06X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, hydrocephaly, fetus 2
O35.07X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, not applicable or unspecified
O35.07X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, fetus 1
O35.07X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, microcephaly, fetus 2
O35.08X0	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, not applicable or unspecified
O35.08X1	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, fetus 1
O35.08X2	Maternal care for (suspected) central nervous system malformation or damage in fetus, spina bifida, fetus 2
O35.09X0	Maternal care for (suspected) other central nervous system malformation or damage in fetus, not applicable or unspecified
O35.09X1	Maternal care for (suspected) other central nervous system malformation or damage in fetus, fetus 1
O35.09X2	Maternal care for (suspected) other central nervous system malformation or damage in fetus, fetus 2
O35.10X0	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, not applicable or unspecified
O35.10X1	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 1
O35.10X2	Maternal care for (suspected) chromosomal abnormality in fetus, unspecified, fetus 2
O35.11X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, not applicable or unspecified
O35.11X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 1
O35.11X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 13, fetus 2
O35.12X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, not applicable or unspecified
O35.12X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 1

ICD-10-CM Diagnosis Codes	Description
O35.12X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 18, fetus 2
O35.13X0	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, not applicable or unspecified
O35.13X1	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 1
O35.13X2	Maternal care for (suspected) chromosomal abnormality in fetus, Trisomy 21, fetus 2
O35.14X0	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, not applicable or unspecified
O35.14X1	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 1
O35.14X2	Maternal care for (suspected) chromosomal abnormality in fetus, Turner Syndrome, fetus 2
O35.15X0	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, not applicable or unspecified
O35.15X1	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 1
O35.15X2	Maternal care for (suspected) chromosomal abnormality in fetus, sex chromosome abnormality, fetus 2
O35.19X0	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, not applicable or unspecified
O35.19X1	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 1
O35.19X2	Maternal care for (suspected) chromosomal abnormality in fetus, other chromosomal abnormality, fetus 2
O35.1XX0	Maternal care for (suspected) chromosomal abnormality in fetus, not applicable or unspecified (Code invalid 09/30/2022)
O35.1XX1	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 1 (Code invalid 09/30/2022)
O35.1XX2	Maternal care for (suspected) chromosomal abnormality in fetus, fetus 2 (Code invalid 09/30/2022)
O35.AXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, not applicable or unspecified
O35.AXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 1
O35.AXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal facial anomalies, fetus 2
O35.BXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, not applicable or unspecified
O35.BXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 1
O35.BXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal cardiac anomalies, fetus 2
O35.CXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, not applicable or unspecified
O35.CXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, fetus 1

ICD-10-CM Diagnosis Codes	Description
O35.CXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal pulmonary anomalies, fetus 2
O35.DXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, not applicable or unspecified
O35.DXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, fetus 1
O35.DXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal gastrointestinal anomalies, fetus 2
O35.EXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, not applicable or unspecified
O35.EXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 1
O35.EXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal genitourinary anomalies, fetus 2
O35.FXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, not applicable or unspecified
O35.FXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 1
O35.FXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal musculoskeletal anomalies of trunk, fetus 2
O35.GXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, not applicable or unspecified
O35.GXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 1
O35.GXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal upper extremities anomalies, fetus 2
O35.HXX0	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, not applicable or unspecified
O35.HXX1	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 1
O35.HXX2	Maternal care for other (suspected) fetal abnormality and damage, fetal lower extremities anomalies, fetus 2
O35.2XX0	Maternal care for (suspected) hereditary disease in fetus, not applicable or unspecified
O35.2XX1	Maternal care for (suspected) hereditary disease in fetus, fetus 1
O35.2XX2	Maternal care for (suspected) hereditary disease in fetus, fetus 2
O35.3XX0	Maternal care for (suspected) damage to fetus from viral disease in mother, not applicable or unspecified
O35.3XX1	Maternal care for (suspected) damage to fetus from viral disease in mother, fetus 1
O35.3XX2	Maternal care for (suspected) damage to fetus from viral disease in mother, fetus 2
O35.4XX0	Maternal care for (suspected) damage to fetus from alcohol, not applicable or unspecified
O35.4XX1	Maternal care for (suspected) damage to fetus from alcohol, fetus 1
O35.4XX2	Maternal care for (suspected) damage to fetus from alcohol, fetus 2
O35.5XX0	Maternal care for (suspected) damage to fetus by drugs, not applicable or unspecified
O35.5XX1	Maternal care for (suspected) damage to fetus by drugs, fetus 1

ICD-10-CM Diagnosis Codes	Description
O35.5XX2	Maternal care for (suspected) damage to fetus by drugs, fetus 2
O35.6XX0	Maternal care for (suspected) damage to fetus by radiation, not applicable or unspecified
O35.6XX1	Maternal care for (suspected) damage to fetus by radiation, fetus 1
O35.6XX2	Maternal care for (suspected) damage to fetus by radiation, fetus 2
O35.7XX0	Maternal care for (suspected) damage to fetus by other medical procedures, not applicable or unspecified
O35.7XX1	Maternal care for (suspected) damage to fetus by other medical procedures, fetus 1
O35.7XX2	Maternal care for (suspected) damage to fetus by other medical procedures, fetus 2
O35.8XX0	Maternal care for other (suspected) fetal abnormality and damage, not applicable or unspecified
O35.8XX1	Maternal care for other (suspected) fetal abnormality and damage, fetus 1
O35.8XX2	Maternal care for other (suspected) fetal abnormality and damage, fetus 2
O35.9XX0	Maternal care for (suspected) fetal abnormality and damage, unspecified, not applicable or unspecified
O35.9XX1	Maternal care for (suspected) fetal abnormality and damage, unspecified, fetus 1
O35.9XX2	Maternal care for (suspected) fetal abnormality and damage, unspecified, fetus 2
O36.20X0	Maternal care for hydrops fetalis, unspecified trimester, not applicable or unspecified
O36.20X1	Maternal care for hydrops fetalis, unspecified trimester, fetus 1
O36.20X2	Maternal care for hydrops fetalis, unspecified trimester, fetus 2
O36.21X0	Maternal care for hydrops fetalis, first trimester, not applicable or unspecified
O36.21X1	Maternal care for hydrops fetalis, first trimester, fetus 1
O36.21X2	Maternal care for hydrops fetalis, first trimester, fetus 2
O36.22X0	Maternal care for hydrops fetalis, second trimester, not applicable or unspecified
O36.22X1	Maternal care for hydrops fetalis, second trimester, fetus 1
O36.22X2	Maternal care for hydrops fetalis, second trimester, fetus 2
O36.23X0	Maternal care for hydrops fetalis, third trimester, not applicable or unspecified
O36.23X1	Maternal care for hydrops fetalis, third trimester, fetus 1
O36.23X2	Maternal care for hydrops fetalis, third trimester, fetus 2
O36.5110	Maternal care for known or suspected placental insufficiency, first trimester, not applicable or unspecified
O36.5111	Maternal care for known or suspected placental insufficiency, first trimester, fetus 1
O36.5112	Maternal care for known or suspected placental insufficiency, first trimester, fetus 2
O36.5120	Maternal care for known or suspected placental insufficiency, second trimester, not applicable or unspecified
O36.5121	Maternal care for known or suspected placental insufficiency, second trimester, fetus 1
O36.5122	Maternal care for known or suspected placental insufficiency, second trimester, fetus 2
O36.5130	Maternal care for known or suspected placental insufficiency, third trimester, not applicable or unspecified
O36.5131	Maternal care for known or suspected placental insufficiency, third trimester, fetus 1

ICD-10-CM Diagnosis Codes	Description
O36.5132	Maternal care for known or suspected placental insufficiency, third trimester, fetus 2
O36.5190	Maternal care for known or suspected placental insufficiency, unspecified trimester, not applicable or unspecified
O36.5191	Maternal care for known or suspected placental insufficiency, unspecified trimester, fetus 1
O36.5192	Maternal care for known or suspected placental insufficiency, unspecified trimester, fetus 2
O36.5910	Maternal care for other known or suspected poor fetal growth, first trimester, not applicable or unspecified
O36.5911	Maternal care for other known or suspected poor fetal growth, first trimester, fetus 1
O36.5912	Maternal care for other known or suspected poor fetal growth, first trimester, fetus 2
O36.5920	Maternal care for other known or suspected poor fetal growth, second trimester, not applicable or unspecified
O36.5921	Maternal care for other known or suspected poor fetal growth, second trimester, fetus 1
O36.5922	Maternal care for other known or suspected poor fetal growth, second trimester, fetus 2
O36.5930	Maternal care for other known or suspected poor fetal growth, third trimester, not applicable or unspecified
O36.5931	Maternal care for other known or suspected poor fetal growth, third trimester, fetus 1
O36.5932	Maternal care for other known or suspected poor fetal growth, third trimester, fetus 2
O36.5990	Maternal care for other known or suspected poor fetal growth, unspecified trimester, not applicable or unspecified
O36.5991	Maternal care for other known or suspected poor fetal growth, unspecified trimester, fetus 1
O36.5992	Maternal care for other known or suspected poor fetal growth, unspecified trimester, fetus 2
O36.60X0	Maternal care for excessive fetal growth, unspecified trimester, not applicable or unspecified
O36.60X1	Maternal care for excessive fetal growth, unspecified trimester, fetus 1
O36.60X2	Maternal care for excessive fetal growth, unspecified trimester, fetus 2
O36.61X0	Maternal care for excessive fetal growth, first trimester, not applicable or unspecified
O36.61X1	Maternal care for excessive fetal growth, first trimester, fetus 1
O36.61X2	Maternal care for excessive fetal growth, first trimester, fetus 2
O36.62X0	Maternal care for excessive fetal growth, second trimester, not applicable or unspecified
O36.62X1	Maternal care for excessive fetal growth, second trimester, fetus 1
O36.62X2	Maternal care for excessive fetal growth, second trimester, fetus 2
O36.63X0	Maternal care for excessive fetal growth, third trimester, not applicable or unspecified
O36.63X1	Maternal care for excessive fetal growth, third trimester, fetus 1
O36.63X2	Maternal care for excessive fetal growth, third trimester, fetus 2

ICD-10-CM Diagnosis Codes	Description
O36.70X0	Maternal care for viable fetus in abdominal pregnancy, unspecified trimester, not applicable or unspecified
O36.70X1	Maternal care for viable fetus in abdominal pregnancy, unspecified trimester, fetus 1
O36.70X2	Maternal care for viable fetus in abdominal pregnancy, unspecified trimester, fetus 2
O36.71X0	Maternal care for viable fetus in abdominal pregnancy, first trimester, not applicable or unspecified
O36.71X1	Maternal care for viable fetus in abdominal pregnancy, first trimester, fetus 1
O36.71X2	Maternal care for viable fetus in abdominal pregnancy, first trimester, fetus 2
O36.72X0	Maternal care for viable fetus in abdominal pregnancy, second trimester, not applicable or unspecified
O36.72X1	Maternal care for viable fetus in abdominal pregnancy, second trimester, fetus 1
O36.72X2	Maternal care for viable fetus in abdominal pregnancy, second trimester, fetus 2
O36.73X0	Maternal care for viable fetus in abdominal pregnancy, third trimester, not applicable or unspecified
O36.73X1	Maternal care for viable fetus in abdominal pregnancy, third trimester, fetus 1
O36.73X2	Maternal care for viable fetus in abdominal pregnancy, third trimester, fetus 2
O36.8120	Decreased fetal movements, second trimester, not applicable or unspecified
O36.8121	Decreased fetal movements, second trimester, fetus 1
O36.8122	Decreased fetal movements, second trimester, fetus 2
O36.8130	Decreased fetal movements, third trimester, not applicable or unspecified
O36.8131	Decreased fetal movements, third trimester, fetus 1
O36.8132	Decreased fetal movements, third trimester, fetus 2
O36.8190	Decreased fetal movements, unspecified trimester, not applicable or unspecified
O36.8191	Decreased fetal movements, unspecified trimester, fetus 1
O36.8192	Decreased fetal movements, unspecified trimester, fetus 2
O36.8310	Maternal care for abnormalities of the fetal heart rate or rhythm, first trimester, not applicable or unspecified
O36.8311	Maternal care for abnormalities of the fetal heart rate or rhythm, first trimester, fetus 1
O36.8312	Maternal care for abnormalities of the fetal heart rate or rhythm, first trimester, fetus 2
O36.8320	Maternal care for abnormalities of the fetal heart rate or rhythm, second trimester, not applicable or unspecified
O36.8321	Maternal care for abnormalities of the fetal heart rate or rhythm, second trimester, fetus 1
O36.8322	Maternal care for abnormalities of the fetal heart rate or rhythm, second trimester, fetus 2
O36.8330	Maternal care for abnormalities of the fetal heart rate or rhythm, third trimester, not applicable or unspecified
O36.8331	Maternal care for abnormalities of the fetal heart rate or rhythm, third trimester, fetus 1
O36.8332	Maternal care for abnormalities of the fetal heart rate or rhythm, third trimester, fetus 2
O36.8390	Maternal care for abnormalities of the fetal heart rate or rhythm, unspecified trimester, not applicable or unspecified

ICD-10-CM Diagnosis Codes	Description
O36.8391	Maternal care for abnormalities of the fetal heart rate or rhythm, unspecified trimester, fetus 1
O36.8392	Maternal care for abnormalities of the fetal heart rate or rhythm, unspecified trimester, fetus 2
O36.8910	Maternal care for other specified fetal problems, first trimester, not applicable or unspecified
O36.8911	Maternal care for other specified fetal problems, first trimester, fetus 1
O36.8912	Maternal care for other specified fetal problems, first trimester, fetus 2
O36.8920	Maternal care for other specified fetal problems, second trimester, not applicable or unspecified
O36.8921	Maternal care for other specified fetal problems, second trimester, fetus 1
O36.8922	Maternal care for other specified fetal problems, second trimester, fetus 2
O36.8930	Maternal care for other specified fetal problems, third trimester, not applicable or unspecified
O36.8931	Maternal care for other specified fetal problems, third trimester, fetus 1
O36.8932	Maternal care for other specified fetal problems, third trimester, fetus 2
O36.8990	Maternal care for other specified fetal problems, unspecified trimester, not applicable or unspecified
O36.8991	Maternal care for other specified fetal problems, unspecified trimester, fetus 1
O36.8992	Maternal care for other specified fetal problems, unspecified trimester, fetus 2
O36.90X0	Maternal care for fetal problem, unspecified, unspecified trimester, not applicable or unspecified
O36.90X1	Maternal care for fetal problem, unspecified, unspecified trimester, fetus 1
O36.90X2	Maternal care for fetal problem, unspecified, unspecified trimester, fetus 2
O36.91X0	Maternal care for fetal problem, unspecified, first trimester, not applicable or unspecified
O36.91X1	Maternal care for fetal problem, unspecified, first trimester, fetus 1
O36.91X2	Maternal care for fetal problem, unspecified, first trimester, fetus 2
O36.92X0	Maternal care for fetal problem, unspecified, second trimester, not applicable or unspecified
O36.92X1	Maternal care for fetal problem, unspecified, second trimester, fetus 1
O36.92X2	Maternal care for fetal problem, unspecified, second trimester, fetus 2
O36.93X0	Maternal care for fetal problem, unspecified, third trimester, not applicable or unspecified
O36.93X1	Maternal care for fetal problem, unspecified, third trimester, fetus 1
O36.93X2	Maternal care for fetal problem, unspecified, third trimester, fetus 2
O40.1XX0	Polyhydramnios, first trimester, not applicable or unspecified
O40.1XX1	Polyhydramnios, first trimester, fetus 1
O40.1XX2	Polyhydramnios, first trimester, fetus 2
O40.2XX0	Polyhydramnios, second trimester, not applicable or unspecified
O40.2XX1	Polyhydramnios, second trimester, fetus 1
O40.2XX2	Polyhydramnios, second trimester, fetus 2
O40.3XX0	Polyhydramnios, third trimester, not applicable or unspecified
O40.3XX1	Polyhydramnios, third trimester, fetus 1
O40.3XX2	Polyhydramnios, third trimester, fetus 2
O40.9XX0	Polyhydramnios, unspecified trimester, not applicable or unspecified
O40.9XX1	Polyhydramnios, unspecified trimester, fetus 1
O40.9XX2	Polyhydramnios, unspecified trimester, fetus 2

ICD-10-CM Diagnosis Codes	Description
O41.00X0	Oligohydramnios, unspecified trimester, not applicable or unspecified
O41.00X1	Oligohydramnios, unspecified trimester, fetus 1
O41.00X2	Oligohydramnios, unspecified trimester, fetus 2
O41.01X0	Oligohydramnios, first trimester, not applicable or unspecified
O41.01X1	Oligohydramnios, first trimester, fetus 1
O41.01X2	Oligohydramnios, first trimester, fetus 2
O41.02X0	Oligohydramnios, second trimester, not applicable or unspecified
O41.02X1	Oligohydramnios, second trimester, fetus 1
O41.02X2	Oligohydramnios, second trimester, fetus 2
O41.03X0	Oligohydramnios, third trimester, not applicable or unspecified
O41.03X1	Oligohydramnios, third trimester, fetus 1
O41.03X2	Oligohydramnios, third trimester, fetus 2
O41.1010	Infection of amniotic sac and membranes, unspecified, first trimester, not applicable or unspecified
O41.1011	Infection of amniotic sac and membranes, unspecified, first trimester, fetus 1
O41.1012	Infection of amniotic sac and membranes, unspecified, first trimester, fetus 2
O41.1020	Infection of amniotic sac and membranes, unspecified, second trimester, not applicable or unspecified
O41.1021	Infection of amniotic sac and membranes, unspecified, second trimester, fetus 1
O41.1022	Infection of amniotic sac and membranes, unspecified, second trimester, fetus 2
O41.1030	Infection of amniotic sac and membranes, unspecified, third trimester, not applicable or unspecified
O41.1031	Infection of amniotic sac and membranes, unspecified, third trimester, fetus 1
O41.1032	Infection of amniotic sac and membranes, unspecified, third trimester, fetus 2
O41.1090	Infection of amniotic sac and membranes, unspecified, unspecified trimester, not applicable or unspecified
O41.1091	Infection of amniotic sac and membranes, unspecified, unspecified trimester, fetus 1
O41.1092	Infection of amniotic sac and membranes, unspecified, unspecified trimester, fetus 2
O41.1210	Chorioamnionitis, first trimester, not applicable or unspecified
O41.1211	Chorioamnionitis, first trimester, fetus 1
O41.1212	Chorioamnionitis, first trimester, fetus 2
O41.1220	Chorioamnionitis, second trimester, not applicable or unspecified
O41.1221	Chorioamnionitis, second trimester, fetus 1
O41.1222	Chorioamnionitis, second trimester, fetus 2
O41.1230	Chorioamnionitis, third trimester, not applicable or unspecified
O41.1231	Chorioamnionitis, third trimester, fetus 1
O41.1232	Chorioamnionitis, third trimester, fetus 2
O41.1290	Chorioamnionitis, unspecified trimester, not applicable or unspecified
O41.1291	Chorioamnionitis, unspecified trimester, fetus 1
O41.1292	Chorioamnionitis, unspecified trimester, fetus 2
O41.1410	Placentitis, first trimester, not applicable or unspecified
O41.1411	Placentitis, first trimester, fetus 1
O41.1412	Placentitis, first trimester, fetus 2
O41.1420	Placentitis, second trimester, not applicable or unspecified
O41.1421	Placentitis, second trimester, fetus 1
O41.1422	Placentitis, second trimester, fetus 2

ICD-10-CM Diagnosis Codes	Description
O41.1430	Placentitis, third trimester, not applicable or unspecified
O41.1431	Placentitis, third trimester, fetus 1
O41.1432	Placentitis, third trimester, fetus 2
O41.1490	Placentitis, unspecified trimester, not applicable or unspecified
O41.1491	Placentitis, unspecified trimester, fetus 1
O41.1492	Placentitis, unspecified trimester, fetus 2
O41.8X10	Other specified disorders of amniotic fluid and membranes, first trimester, not applicable or unspecified
O41.8X11	Other specified disorders of amniotic fluid and membranes, first trimester, fetus 1
O41.8X12	Other specified disorders of amniotic fluid and membranes, first trimester, fetus 2
O41.8X20	Other specified disorders of amniotic fluid and membranes, second trimester, not applicable or unspecified
O41.8X21	Other specified disorders of amniotic fluid and membranes, second trimester, fetus 1
O41.8X22	Other specified disorders of amniotic fluid and membranes, second trimester, fetus 2
O41.8X30	Other specified disorders of amniotic fluid and membranes, third trimester, not applicable or unspecified
O41.8X31	Other specified disorders of amniotic fluid and membranes, third trimester, fetus 1
O41.8X32	Other specified disorders of amniotic fluid and membranes, third trimester, fetus 2
O41.8X90	Other specified disorders of amniotic fluid and membranes, unspecified trimester, not applicable or unspecified
O41.8X91	Other specified disorders of amniotic fluid and membranes, unspecified trimester, fetus 1
O41.8X92	Other specified disorders of amniotic fluid and membranes, unspecified trimester, fetus 2
O41.90X0	Disorder of amniotic fluid and membranes, unspecified, unspecified trimester, not applicable or unspecified
O41.90X1	Disorder of amniotic fluid and membranes, unspecified, unspecified trimester, fetus 1
O41.90X2	Disorder of amniotic fluid and membranes, unspecified, unspecified trimester, fetus 2
O41.91X0	Disorder of amniotic fluid and membranes, unspecified, first trimester, not applicable or unspecified
O41.91X1	Disorder of amniotic fluid and membranes, unspecified, first trimester, fetus 1
O41.91X2	Disorder of amniotic fluid and membranes, unspecified, first trimester, fetus 2
O41.92X0	Disorder of amniotic fluid and membranes, unspecified, second trimester, not applicable or unspecified
O41.92X1	Disorder of amniotic fluid and membranes, unspecified, second trimester, fetus 1
O41.92X2	Disorder of amniotic fluid and membranes, unspecified, second trimester, fetus 2
O41.93X0	Disorder of amniotic fluid and membranes, unspecified, third trimester, not applicable or unspecified
O41.93X1	Disorder of amniotic fluid and membranes, unspecified, third trimester, fetus 1
O41.93X2	Disorder of amniotic fluid and membranes, unspecified, third trimester, fetus 2

ICD-10-CM Diagnosis Codes	Description
O43.011-O43.019	Fetomaternal placental transfusion syndrome
O43.101-O43.109	Malformation of placenta, unspecified
O43.111-O43.119	Circumvallate placenta
O43.121-O43.129	Velamentous insertion of umbilical cord
O43.191-O43.199	Other malformation of placenta
O43.211-O43.219	Placenta accreta
O43.221-O43.229	Placenta increta
O43.231-O43.239	Placenta percreta
O43.811-O43.819	Placental infarction
O43.891-O43.899	Other placental disorders
O43.90-O43.93	Unspecified placental disorder
O44.00-O44.03	Complete placenta previa NOS or without hemorrhage
O44.10-O44.13	Complete placenta previa with hemorrhage
O44.20-O44.23	Partial placenta previa NOS or without hemorrhage
O44.30-O44.33	Partial placenta previa with hemorrhage
O44.40-O44.43	Low lying placenta NOS or without hemorrhage
O44.50-O44.53	Low lying placenta with hemorrhage
O45.001-O45.009	Premature separation of placenta with coagulation defect
O45.011-O45.019	Premature separation of placenta with afibrinogenemia
O45.021-O45.029	Premature separation of placenta with disseminated intravascular coagulation
O45.091-O45.099	Premature separation of placenta with other coagulation defect
O45.8X1-O45.8X9	Other premature separation of placenta
O45.90-O45.93	Premature separation of placenta, unspecified
O46.001-O46.009	Antepartum hemorrhage with coagulation defect, unspecified

ICD-10-CM Diagnosis Codes	Description
O46.011-O46.019	Antepartum hemorrhage with afibrinogenemia
O46.021-O46.029	Antepartum hemorrhage with disseminated intravascular coagulation
O46.091-O46.099	Antepartum hemorrhage with other coagulation defect
O46.8X1-O46.8X9	Other antepartum hemorrhage
O46.90-O46.93	Antepartum hemorrhage, unspecified
O47.00	False labor before 37 completed weeks of gestation, unspecified trimester
O47.02	False labor before 37 completed weeks of gestation, second trimester
O47.03	False labor before 37 completed weeks of gestation, third trimester
O47.1	False labor at or after 37 completed weeks of gestation
O47.9	False labor, unspecified
O48.0	Post-term pregnancy
O48.1	Prolonged pregnancy
O60.00	Preterm labor without delivery, unspecified trimester
O60.02	Preterm labor without delivery, second trimester
O60.03	Preterm labor without delivery, third trimester
O98.011-O98.019	Tuberculosis complicating pregnancy
O98.111-O98.119	Syphilis complicating pregnancy
O98.211-O98.219	Gonorrhea complicating pregnancy
O98.311-O98.319	Other infections with a predominantly sexual mode of transmission complicating pregnancy
O98.411-O98.419	Viral hepatitis complicating pregnancy
O98.511-O98.519	Other viral diseases complicating pregnancy
O98.611-O98.619	Protozoal diseases complicating pregnancy
O98.711-O98.719	Human immunodeficiency virus [HIV] disease complicating pregnancy
O98.811-O98.819	Other maternal infectious and parasitic diseases complicating pregnancy
O98.911-O98.919	Unspecified maternal infectious and parasitic disease complicating pregnancy
O99.011-O99.019	Anemia complicating pregnancy
O99.111-O99.119	Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating pregnancy
O99.210-O99.213	Obesity complicating pregnancy
O99.280-O99.283	Endocrine, nutritional and metabolic diseases complicating pregnancy

ICD-10-CM Diagnosis Codes	Description
O99.310-O99.313	Alcohol use complicating pregnancy
O99.320-O99.323	Drug use complicating pregnancy
O99.330-O99.333	Smoking (tobacco) complicating pregnancy
O99.340-O99.343	Other mental disorders complicating pregnancy
O99.350-O99.353	Diseases of the nervous system complicating pregnancy
O99.411-O99.419	Diseases of the circulatory system complicating pregnancy
O99.511-O99.519	Diseases of the respiratory system complicating pregnancy
O99.611-O99.619	Diseases of the digestive system complicating pregnancy
O99.711-O99.719	Diseases of the skin and subcutaneous tissue complicating pregnancy
O99.810	Abnormal glucose complicating pregnancy
O99.820	Streptococcus B carrier state complicating pregnancy
O99.830	Other infection carrier state complicating pregnancy
O99.840-O99.843	Bariatric surgery status complicating pregnancy
O99.891	Other specified diseases and conditions complicating pregnancy
O9A.111-O9A.119	Malignant neoplasm complicating pregnancy
O9A.211-O9A.219	Injury, poisoning and certain other consequences of external causes complicating pregnancy
O9A.311-O9A.319	Physical abuse complicating pregnancy
O9A.411-O9A.419	Sexual abuse complicating pregnancy
O9A.511-O9A.519	Psychological abuse complicating pregnancy
Z34.00-Z34.03	Encounter for supervision of normal first pregnancy
Z34.80-Z34.83	Encounter for supervision of other normal pregnancy
Z34.90-Z34.93	Encounter for supervision of normal pregnancy, unspecified
Z36.0-Z36.4	Encounter for antenatal screening of mother
Z36.81-Z36.9	Encounter for other antenatal screening
Z3A.00	Weeks of gestation of pregnancy not specified
Z3A.10-Z3A.19	Weeks of gestation of pregnancy, weeks 10-19
Z3A.20-Z3A.29	Weeks of gestation of pregnancy, weeks 20-29

ICD-10-CM Diagnosis Codes	Description
Z3A.30-Z3A.39	Weeks of gestation of pregnancy, weeks 30-39
Z3A.40-Z3A.49	Weeks of gestation of pregnancy, weeks 40 or greater

Not Covered or Reimbursable:

ICD-10-CM Diagnosis Codes	Description
	All other diagnosis codes

Not Covered or Reimbursable:

CPT® Codes	Description
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
0341U	Fetal aneuploidy DNA sequencing comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploid

Invasive Prenatal Testing of a Fetus

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
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
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)

CPT®* Codes	Description
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons

†**Note: Considered Experimental/Investigational/Unproven when used to report genetic mutation reproductive genetic testing for recurrent pregnancy loss.**
Considered Not Medically Necessary when used to report preimplantation genetic screening for common aneuploidy.

Germline Mutation Reproductive Genetic Testing for Recurrent Pregnancy Loss

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
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
88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding

Considered Not Medically Necessary:

CPT®* Codes	Description
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81400†	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)

†**Note: Considered not medically necessary when used to report PAI-1 gene testing in the evaluation of recurrent pregnancy loss.**

Germline Mutation Reproductive Genetic Testing for Infertility

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants

CPT®* Codes	Description
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
88280	Chromosome analysis; additional karyotypes, each study
89329	Sperm evaluation; hamster penetration test

Not Covered or Reimbursable when used to report sperm DNA integrity testing:

CPT®* Codes	Description
88182	Flow cytometry, cell cycle or DNA analysis

References

1. Abbaszadegan MR, Keify F, Ashrafzadeh F, Farshchian M, Khadivi-Zand F, Teymoorzadeh MN, et al. Gene dosage analysis of proximal spinal muscular atrophy carriers using real-time PCR. Arch Iran Med. 2011 May;14(3):188-91.

2. Abbs S, Tuffery-Giraud S, Bakker E, Ferlini A, Sejersen T, Mueller CR. Best practice guidelines on molecular diagnostics in Duchenne/Becker muscular dystrophies. Neuromuscul Disord. 2010 Jun;20(6):422-7.

3. Altarescu G, Eldar-Geva T, Brooks B, Zylber-Haran E, Varshaver I, Margalioth EJ, et al. Preimplantation genetic diagnosis (PGD) for nonsyndromic deafness by polar body and blastomere biopsy. J Assist Reprod Genet. 2009 Jul;26(7):391-7.

4. American Board of Medical Genetics and Genomics. About the ABMGG. Accessed Nov 10, 2023. Available at URL address: http://www.abmgg.org/

5. American College of Medical Genetics and Genomics (ACMG). ©2023 American College of Medical Genetics and Genomics. Accessed Nov 10, 2023. Available at URL address: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/Practice_Resources/ACMG/Medical-Genetics-Practice-Resources/Medical-Genetics-Practice-Resources.aspx?hkey=d56a0de8-cfb0-4c6e-bf1e-ffb96e5f86aa

6. American College of Obstetricians and Gynecologists (ACOG). ©2023. Committee Opinion No. 690 (Mar 2017, reaffirmed 2023). Carrier screening in the age of genomic medicine. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-in-the-age-of-genomic-medicine

7. American College of Obstetricians and Gynecologists (ACOG). ©2023. Committee on Genetics. Committee Opinion No. 691: Mar 2017. Reaffirmed 2023. Carrier Screening for Genetic Conditions. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-for-genetic-conditions

8. American College of Obstetricians and Gynecologists (ACOG). ©2023. Committee on Genetics. Committee Opinion No. 693: Counseling about genetic testing and communication of genetic test results. Apr 2017. Reaffirmed 2020. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/04/counseling-about-genetic-testing-and-communication-of-genetic-test-results

9. American College of Obstetricians and Gynecologists (ACOG)/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. Dec 2016. Reaffirmed 2023. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2016/12/microarrays-and-next-generation-sequencing-technology-the-use-of-advanced-genetic-diagnostic-tools-in-obstetrics-and-gynecology

10. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 78. Jan 2007. Updated Aug 2022. Hemoglobinopathies in Pregnancy. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2022/08/hemoglobinopathies-in-pregnancy#

11. American College of Obstetricians and Gynecologists (ACOG). ©2023. Committee on Obstetrics. Practice Bulletin No. 197. Inherited thrombophilias in pregnancy. 2018 Jul. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/07/inherited-thrombophilias-in-pregnancy

12. American College of Obstetricians and Gynecologists (ACOG). ©2023. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 196. Thromboembolism in pregnancy. 2018 Jul. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/07/thromboembolism-in-pregnancy

13. American College of Obstetricians and Gynecologists (ACOG)/The Society for Maternal-Fetal Medicine. Practice Bulletin No. 162. Prenatal diagnostic testing for genetic disorders. 2016 May. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2016/05/prenatal-diagnostic-testing-for-genetic-disorders

14. American Congress of Obstetricians and Gynecologists. Practice Bulletin No. 226 (Oct 2020, replaces Practice Bulletin 163) Screening for fetal chromosomal abnormalities. Accessed Nov 10, 2023. Available at URL address: https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2020/10/screening-for-fetal-chromosomal-abnormalities

15. American Society for Reproductive Medicine (ASRM). A Practice Committee Opinion. Definitions of infertility and recurrent pregnancy loss. ©2013 American Society for Reproductive Medicine. Fertil Steril. 2013 Jan;99(1):63.

16. American Society for Reproductive Medicine (ASRM). A Practice Committee Educational Bulletin. Optimal Evaluation of the Infertile Male: a committee opinion. Fertil Steril 2012e:98:294-301.

17. American Society of Reproductive Medicine (ASRM). Preimplantation genetic testing: a Practice Committee opinion. Practice Committee of the Society for Assisted Reproductive Technology; Practice Committee of the American Society for Reproductive Medicine. Fertil Steril. ©2008 American Society for Reproductive Medicine. Fertil Steril. 2008j Nov;90(5 Suppl):S136-43.

18. American Society for Reproductive Medicine (ASRM). The Clinical Utility of Sperm DNA Integrity Testing: A guideline. The Practice Committee of the ASRM. Fertil Steril 99:3; March 2013, p 673-677.

19. Armengol L, Nevado J, Serra-Juhé C, et al. Clinical utility of chromosomal microarray analysis in invasive prenatal diagnosis. Hum Genet. 2012;131(3):513-523.

20. Ashoor G, Syngelaki A, Wagner M, Birdir C, Nicolaides KH. Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18. Am J Obstet Gynecol. 2012 Apr;206(4):322.e1-5.

21. Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, et al. Clinical guidelines for testing for heritable thrombophilia. Br. J Haematol. 2010 Apr;149(2): 209-20.

22. Bajaj PS, Veenstra DL. A risk-benefit analysis of factor V Leiden testing to improve pregnancy outcomes: a case study of the capabilities of decision modeling in genomics. Genet Med. 2013 May;15(5):374-81.

23. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO;American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy,and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.Chest. 2012 Feb;141(2 Suppl):e691S-736S.

24. Benn P, Borrell A, Crossley J, Cuckle H, Dugoff L, Gross S, et al. Aneuploidy screening: a position statement from a committee on behalf of the Board of the International Society for Prenatal Diagnosis, January 2011. Prenat Diagn. 2011 Jun;31(6):519-22.

25. Bianchi DW, Parker RL, Wentworth J, Madankumar R, Saffer C, Das AF, et al. DNA sequencing versus standard prenatal aneuploidy screening. N Engl J Med. 2014 Feb 27;370(9):799-808.

26. Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP; MatErnal BLood IS Source to Accurately diagnose fetal aneuploidy (MELISSA) Study Group. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. Obstet Gynecol. 2012 May;119(5):890-901.

27. Bick DP, Lau EC. Preimplantation genetic diagnosis. Pediatr Clin North Am. 2006 Aug;53(4):559-77.

28. Biron-Andreani C, Bauters A, Le Cam-Duchez V, Delahousse B, Lequerrec A, Dutrillaux F, et al. Factor v leiden homozygous genotype and pregnancy outcomes. Obstetrics & Gynecology. 2009 Dec;114(6):1249-53.

29. Bloomenthal D, von Dadelszen P, Liston R, Magee L, Tsang P. The effect of factor V Leiden carriage on maternal and fetal health. CMAJ. 2002 Jul 9;167(1):48-54.

30. Botta A, Bonifazi E, Vallo L, Gennarelli M, Garrè C, Salehi L, et al. Italian guidelines for molecular analysis in myotonic dystrophies. Acta Myol. 2006 Jun;25(1):23-33.

31. Bradley LA, Palomaki GE, Bienstock J, VArga E, Scott JA. Can factor V Leiden and prothrombin G20210A testing in women with recurrent pregnancy loss result in improved pregnancy outcomes? Results from a targeted evidence-based review. Genet Med. 2012 Jan;14(1):39-50. Epub 2011 Sep 13.

32. Brezina PR, Kutteh WH2. Clinical applications of preimplantation genetic testing. BMJ. 2015 Feb 19;350:g7611.

33. Calvo SE, Compton AG, Hershman SG, Lim SC, Lieber DS, Tucker EJ, Laskowski A, Garone C, Liu S, Jaffe DB, Christodoulou J, Fletcher JM, Bruno DL, Goldblatt J, Dimauro S, Thorburn DR, Mootha VK. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. Sci Transl Med. 2012 Jan 25;4(118):118ra10.

34. Canick JA, Kloza EM, Lambert-Messerlian GM, Haddow JE, Ehrich M, van den Boom D, et al. DNA sequencing of maternal plasma to identify Down syndrome and other trisomies in multiple gestations. Prenat Diagn. 2012 Aug;32(8):730-4. Epub 2012 May 14.

35. Carp HJ. Thrombophilia and recurrent pregnancy loss. Obstet Gynecol Clin North Am. 2006 Sep;33(3):429-42.

36. Chitty LS, Mason S, Barrett AN, et al. Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next-generation sequencing allows for a safer, more accurate, and comprehensive approach. Prenatal Diagnosis. 2015;35(7):656-662.

37. Chiu RW, Akolekar R, Zheng YW, Leung TY, Sun H, Chan KC, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. BMJ. 2011 Jan 11;342:c7401.

38. Cleary-Goldman J, Nakhuda GS, Zimmerman RC, Sauer MV. The role of factor V Leiden mutation in recurrent pregnancy loss. J Am Med Womens Assoc. 2003 Summer;58(3):165-72.

39. Dan S, Yuan Y, Wang Y, et al. Non-Invasive Prenatal Diagnosis of Lethal Skeletal Dysplasia by Targeted Capture Sequencing of Maternal Plasma. Sun HS, ed. PLOS One. 2016;11(7):e0159355.

40. Dashe JS. Aneuploidy Screening in Pregnancy. Obstet Gynecol. 2016 Jul;128(1):181-94. doi: 10.1097/AOG.0000000000001385. PubMed PMID: 27275786.

41. Davenport WB, Kutteh WH. Inherited thrombophilias and adverse pregnancy outcomes. Obstet Gynecol Clin North Am. 2014 Mar;41(1):133-44.

42. Debrock S, Melotte C, Spiessens C, et al. Preimplantation genetic screening for aneuploidy of embryos after in vitro fertilization in women aged at least 35 years: a prospective randomized trial. Fertil Steril. 2010;93(2):364-373.

43. Deignan JL, Astbury C, Cutting GR, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(8):1288-1295.

44. Dequeker E, Stuhrmann M, Morris MA, Casals T, Castellani C, Claustres M, Cuppens H, des Georges M, Ferec C, Macek M, Pignatti PF, Scheffer H, Schwartz M, Witt M, Schwarz M, Girodon E. Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders--updated European recommendations. Eur J Hum Genet. 2009 Jan;17(1):51-65.

45. Dhillon RK, Hillman SC, Morris RK, McMullan D, Williams D, Coomarasamy A, Kilby MD. Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: a systematic review and meta-analysis. BJOG. 2014 Jan;121(1):11-21.

46. Dondorp W, de Wert G, Bombard Y, Bianchi DW, Bergmann C, Borry P, Chitty LS, Fellmann F, Forzano F, Hall A, Henneman L, Howard HC, Lucassen A, Ormond K,Peterlin B, Radojkovic D, Rogowski W, Soller M, Tibben A, Tranebjærg L, van El CG, Cornel MC. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Summary and recommendations. Eur J Hum Genet. 2015 Apr 1.

47. Duhl AJ, Paidas MJ, Ural SH, Branch W, Casele H, Cox-Gill J, Hamersley SL, Hyers TM, Katz V, Kuhlmann R, Nutescu EA, Thorp JA, Zehnder JL; Pregnancy and Thrombosis Working Group. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. Am J Obstet Gynecol. 2007 Nov;197(5):457.e1-21

48. Edenborough FP, Borgo G, Knoop C, Lannefors L, Mackenzie WE, Madge S, Morton AM, Oxley HC, Touw DJ, Benham M, Johannesson M; European Cystic Fibrosis Society. Guidelines for the management of pregnancy in women with cystic fibrosis. J Cyst Fibros. 2008 Jan;7 Suppl 1:S2-32. Epub 2007 Nov 19.

49. Edwards JG. Contemporary genetic counseling. Obstet Gynecol Clin North Am. 2010;37(1):.

50. Edwards JG, Feldman G, Goldberg J, Gregg AR, Norton ME, Rose NC, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol. 2015 Mar;125(3):653-662.

51. Ehrich M, Deciu C, Zwiefelhofer T, Tynan JA, Cagasan L, Tim R, et al. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. Am J Obstet Gynecol. 2011 Mar;204(3):205.e1-11. Epub 2011 Feb 18.

52. Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A. Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the National Society of Genetic Counselors. J Genet Couns. 2012 Dec;21(6):752-60.

53. Fiorentino F, Caiazzo F, Napolitano S, et al. Introducing array comparative genomic hybridization into routine prenatal diagnosis practice: a prospective study on over 1000 consecutive clinical cases. Prenat Diagn. 2011;31(13):1270-1282.

54. Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. 2015 Mar;45(3):249-66.

55. Gordy WW, Griffen JH, Taylor AK, Ko BR, Heit JA. American College of Medical Genetics Consensus Statement on Factor V Leiden Mutation Testing. Genet Med. 2001 Mar/Apr;3(2):139-48.

56. Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG) [published correction appears in Genet Med. 2021 Aug 27;:]. Genet Med. 2021;23(10):1793-1806.

57. Gregg AR, Gross SJ, Best RG, Monaghan KG, Bajaj K, Skotko BG, et al. ACMG statement on noninvasive prenatal screening for fetal aneuploidy. Genet Med. 2013 May;15(5):395-8.

58. Grody WW, Thompson BH, Gregg AR, Bean LH, Monaghan KG, Schneider A, Lebo RV. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med. 2013 Jun;15(6):482-3.

59. Gross SJ, Pletcher BA, Monaghan KG; Professional Practice and Guidelines Committee. Carrier screening in individuals of Ashkenazi Jewish descent. Genet Med. 2008 Jan;10(1):54-6.

60. Hardarson T, Hanson C, Lundin K, et al. Preimplantation genetic screening in women of advanced maternal age caused a decrease in clinical pregnancy rate: a randomized controlled trial. Hum Reprod. 2008;23(12):2806-2812.

61. Harmony™ Prenatal Test. © 2017 F. Hoffman-LaRoche, Ltd. Accessed Sep 27, 2022. Available at URL address: https://www.harmonytest.com/global/en/nipt-test-for-expecting-parents-cell-free-dna.html

62. Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genet Med. 2013 Feb;15(2):153-6.

63. Hillman SC, McMullan DJ, Hall G, et al. Use of prenatal chromosomal microarray: prospective cohort study and systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2013;41(6):610-620.

64. Hogge WA, Prosen TL, Lanasa MC, Huber HA, Reeves MF. Recurrent spontaneous abortion and skewed X-inactivation: is there an association?. Am J Obstet Gynecol. 2007;196(4):.

65. Hone SW, Smith RJ. Genetic screening for hearing loss. Clin Otolaryngol Allied Sci. 2003 Aug;28(4):285-90.

66. International Myotonic Dystrophy Consortium (IDMC). New nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1). Neurology. 2000;54:1218–1221.

67. International Society of Nurses in Genetics. Accessed Sep 27, 2022. Available at URL address: http://www.isong.org/

68. Jenkins LA, Deans ZC, Lewis C, Allen S. Delivering an accredited non-invasive prenatal diagnosis service for monogenic disorders, and recommendations for best practice. Prenat Diagn. 2017 Dec 20.

69. Kaare M, Painter JN, Ulander VM, Kaaja R, Aittomäki K. Sex chromosome characteristics and recurrent miscarriage. Fertil Steril. 2008;90(6):2328-2333.

70. Labcorp. MaterniT21 PLUS. ©2021. Accessed Sep 27, 2022. Available at URL address: https://womenshealth.labcorp.com/patients/pregnancy/maternit21plus?utm_source=dl&utm_medium=rd&utm_campaign=ig

71. Langfelder-Schwind E, Karczeski B, Strecker MN, Redman J, Sugarman EA, Zaleski C, et al. Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2014 Feb;23(1):5-15.

72. Langlois S, Wilson RD; Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC); Prenatal Diagnosis Committee of the Canadian College of Medical Geneticists (CCMG). Carrier screening for genetic disorders in individuals of Ashkenazi Jewish descent. J Obstet Gynaecol Can. 2006 Apr;28(4):324-43.

73. Laurino MY, Bennett RL, Saraiya DS, Baumeister L, Doyle DL, Leppig K, Pettersen B, Resta R, Shields L, Uhrich S, Varga EA, Raskind WH. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2005 Jun;14(3):165-81.

74. Lee CN, Lin SY, Lin CH, Shih JC, Lin TH, Su YN. Clinical utility of array comparative genomic hybridisation for prenatal diagnosis: a cohort study of 3171 pregnancies. BJOG. 2012;119(5):614-625.

75. Leiber DS, Calvo SE, Shanahan K, Slate NG, Liu S, Hershman SG, et al. Targeted exome sequencing of suspected mitochondrial disorders. Neurology. 2013 May 7;80(19):1762-70.

76. Levy B, Sigurjonsson S, Pettersen B, Maisenbacher MK, Hall MP, Demko Z, Lathi RB, Tao R, Aggarwal V, Rabinowitz M. Genomic imbalance in products of conception: single-nucleotide polymorphism chromosomal microarray analysis. Obstet Gynecol. 2014 Aug;124(2 Pt 1):202-9.

77. Mastenbroek S, Twisk M, van Echten-Arends J, et al. In vitro fertilization with preimplantation genetic screening. N Engl J Med. 2007;357(1):9-17

78. Mazloom AR, Džakula Ž, Oeth P, Wang H, Jensen T, Tynan J, McCullough R, Saldivar JS, Ehrich M, van den Boom D, Bombard AT, Maeder M, McLennan G, Meschino W, Palomaki GE, Canick JA, Deciu C. Noninvasive prenatal detection of sex chromosomal aneuploidies by sequencing circulating cell-free DNA from maternal plasma. Prenat Diagn. 2013 Jun;33(6):591-7.

79. Meyer LR, Klipstein S, Hazlett WD, Nasta T, Mangan P, Karande VC. A prospective randomized controlled trial of preimplantation genetic screening in the "good prognosis" patient. Fertil Steril. 2009;91(5):1731-1738.

80. Muralidharan K, Wilson RB, Ogino S, Nagan N, Curtis C, Schrijver I. Population carrier screening for spinal muscular atrophy a position statement of the association for molecular pathology. J Mol Diagn. 2011 Jan;13(1):3-6.

81. Natera. Panorama™ Prenatal Test. © 2023 Natera. Accessed Nov 10, 2023. Available at URL address: https://www.natera.com/

82. National Center for Biotechnology Information (NCBI). GeneReviews. Accessed Nov 10, 2023. Available at URL address: https://www.ncbi.nlm.nih.gov/books/NBK1116/?term=geneReviews

83. National Institutes of Health: Online Mendelian Inheritance in Man (OMIM). ©1966-2019 Johns Hopkins University. Accessed Nov 10, 2023. Available at URL address: http://omim.org/

84. National Institutes of Health (NIH). MedlinePlus. U.S. National Library of Medicine. Accessed Nov 10, 2023. Available at URL address: https://medlineplus.gov/genetics/

85. National Society of Genetic Counselors (NSGC). Accessed Nov 10, 2023. Available at URL address: https://www.nsgc.org/

86. Nicolaides KH, Syngelaki A, Ashoor G, Birdir C, Touzet G. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. Am J Obstet Gynecol. 2012 Nov;207(5):374.e1-6.

87. Nicolaides KH, Syngelaki A, Poon LC, Gil MM, Wright D. First-trimester contingent screening for trisomies 21, 18 and 13 by biomarkers and maternal blood cell-free DNA testing. Fetal Diagn Ther. 2014;35:185-92.

88. Nicolaides KH, Wright D, Poon LC, Syngelaki A, Gil MM. First-trimester contingent screening for trisomy 21 by biomarkers and maternal blood cell-free DNA testing. Ultrasound Obstet Gynecol. 2013 Jul;42(1):41-50.

89. Norton ME, Brar H, Weiss J, Karimi A, Laurent LC, Caughey AB, et al. Non-Invasive Chromosomal Evaluation (NICE) Study: results of a multicenter prospective cohort study for detection of fetal trisomy 21 and trisomy 18. Am J Obstet Gynecol. 2012 Aug;207(2):137.e1-8.

90. Norton ME, Jacobsson B, Swamy GK, Laurent LC, Ranzini AC, Brar H, et al. Cell-free DNA analysis for noninvasive examination of trisomy. N Engl J Med. 2015 Apr 23;372(17):1589-97.

91. Palomaki GE, Deciu C, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, et al. DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study. Genet Med. 2012 Mar;14(3):296-305.

92. Park NJ, Morgan C, Sharma R, Li Y, Lobo RM, Redman JB, et al. Improving accuracy of Tay-Sachs carrier screening of the non-Jewish population; analysis of 34 carriers and six late-onset patients with HEXA enzyme and DNA sequence analysis. Pediatr Res. 201 Feb;67(2):217-20.

93. Pasquier E, Bohec C, De Saint Martin L, et al. Strong evidence that skewed X-chromosome inactivation is not associated with recurrent pregnancy loss: an incident paired case control study. Hum Reprod. 2007;22(11):2829-2833.

94. Preimplantation Genetic Testing: ACOG Committee Opinion, Number 799. Obstet Gynecol. 2020;135(3):e133-e137.

95. Prior TW. Carrier screening for spinal muscular atrophy. Genet Med.2008 Nov. 10(11):840-2.

96. Prior TW, Narasimhan N, Sugarman EA, Batish SD, Braastad C. Technical standards and guidelines for spinal muscular atrophy testing. Genet Med. 2011 Jul;13(7):686-94.

97. Ram KT, Klugman SD. Best practices: antenatal screening for common genetic conditions other than aneuploidy. Curr Opin Obstet Gynecol. 2010 Feb 1.

98. Reddy UM, Page GP, Saade GR, et al. Karyotype versus microarray testing for genetic abnormalities after stillbirth. N Engl J Med. 2012;367(23):2185-2193

99. Rodger MA, Betancourt MT, Clark P, et al. The association of factor V leiden and prothrombin gene mutation and placenta-mediated pregnancy complications: a systematic review and meta-analysis of prospective cohort studies. PLoS Med. 2010;7(6):e1000292. Published 2010 Jun 15.

100. Royal College of Obstetricians and Gynaecologists. © 2018. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Green-top Guideline No. 37A. Apr 2014. Accessed Sep 27, 2022. Available at URL address: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37a/

101. Royal College of Obstetricians and Gynaecologists. © 2018. Recurrent miscarriage, investigation and treatment of couples (Green-top Guideline No. 17). Apr 2011. Accessed Nov 10, 2023. Available at URL address: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg17/

102. Rubio C, Bellver J, Rodrigo L, et al. Preimplantation genetic screening using fluorescence in situ hybridization in patients with repetitive implantation failure and advanced maternal age: two randomized trials. Fertil Steril. 2013;99(5):1400-1407.

103. Scott SA, Edelmann L, Liu L, Luo M, Desnick RJ, Kornreich R. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Hum Mutat. 2010 Nov;31(11):1240-50.

104. Shaffer LG, Beaudet AL, Brothman AR, Hirsch B, Levy B, Martin CL, et al.; Working Group of the Laboratory Quality Assurance Committee of the American College of Medical Genetics. Microarray analysis for constitutional cytogenetic abnormalities. Genet Med. 2007 Sep;9(9):654-62.

105. Shaffer LG, Dabell MP, Fisher AJ, et al. Experience with microarray-based comparative genomic hybridization for prenatal diagnosis in over 5000 pregnancies. Prenat Diagn. 2012;32(10):976-985.

106. Schlegel PN, Sigman M, Collura B, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline (2020). Fertil Steril. 2021;115(1):54-61.

107. Sherman S, Pletcher BA, Driscoll PA. Fragile X syndrome: diagnostic and carrier testing. Genet Med. 2005 Oct;7(8):584-7.

108. Sierra S, Stephenson M. Genetics of recurrent pregnancy loss. Semin Reprod Med. 2006 Feb;24(1):17-24.

109. Simón C, Gómez C, Cabanillas S, et al. A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. Reprod Biomed Online. 2020;41(3):402-415.

110. Smith J, Hone S. Genetic screening for deafness. Pediatr Clin North Am. 2003 Apr;50(2):315-9.

111. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. Electronic address: pubs@smfm.org. #36: Prenatal aneuploidy screening using cell-free DNA Am J Obstet Gynecol. 2015 Jun;212(6):711-716.

112. Society for Maternal-Fetal Medicine (SMFM). ©2000-2023. Society for Fetal Maternal Medicine. SMFM Statement: Maternal serum cell-free DNA screening in low risk women. Accessed Nov 10, 2023. Available at URL address: https://www.smfm.org/publications/157-smfm-statement-maternal-serum-cell-free-dna-screening-in-low-risk-women

113. Srinivasan A, Bianchi DW, Huang H, Sehnert AJ, Rava RP. Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. Am J Hum Genet. 2013 Feb 7;92(2):167-76.

114. Staessen C, Platteau P, Van Assche E, et al. Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial. Hum Reprod. 2004;19(12):2849-2858.

115. Stephenson MD, Sierra S. Reproductive outcomes in recurrent pregnancy loss associated with a parental carrier of a structural chromosome rearrangement. Hum Reprod. 2006 Apr;21(4):1076-82.

116. Trent RJ, Webster B, Bowden DK, Gilbert A, Holl PJ, Lindeman R, et al. Complex phenotypes in the haemoglobinopathies: recommendations on screening and DNA testing. Pathology. 2006 Dec;38(6):507-19.

117. Verhoef TI, Hill M, Drury S, et al. Non-invasive prenatal diagnosis (NIPD) for single gene disorders: cost analysis of NIPD and invasive testing pathways. Prenat Diagn. 2016;36(7):636-642.

118. Verweij EJ, van den Oever JM, de Boer MA, Boon EM, Oepkes D. Diagnostic accuracy of noninvasive detection of fetal trisomy 21 in maternal blood: a systematic review. Fetal Diagn Ther. 2012;31(2):81-6.

119. Walsh, J.M.E. and Goldberg, J.D. (2013), Fetal aneuploidy detection by maternal plasma DNA sequencing: a technology assessment. Prenat Diagn, 33: 514-520.

120. Wapner RJ, Babiarz JE, Levy B, et al. Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes. Am J Obstet Gynecol. 2015;212(3):332.e1-332.e3329.

121. Wapner RJ, Martin CL, Levy B, et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med. 2012;367(23):2175-2184.

122. Warburton D, Kline J, Kinney A, Yu CY, Levin B, Brown S. Skewed X chromosome inactivation and trisomic spontaneous abortion: no association. Am J Hum Genet. 2009 Aug;85(2):179-93.

123. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel [published correction appears in Genet Med. 2004 Nov-Dec;6(6):548] [published correction appears in Genet Med. 2005 Apr;7(4):286]. Genet Med. 2004;6(5):387-391.

124. Wilson KL, Czerwinski JL, Hoskovec JM, Noblin SJ, Sullivan CM, Harbison A, et al. NSGC practice guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy. Genet Couns. 2013 Feb;22(1):4-15.

125. Winand R, Hens K, Dondorp W, de Wert G, Moreau Y, Vermeesch JR, Liebaers I, Aerts J. In vitro screening of embryos by whole-genome sequencing: now, in the future or never? Hum Reprod. 2014 Feb 2.

126. Yakin K, Ata B, Ercelen N, Balaban B, Urman B. The effect of preimplantation genetic screening on the probability of live birth in young women with recurrent implantation failure; a nonrandomized parallel group trial. Eur J Obstet Gynecol Reprod Biol. 2008;140(2):224-229.

127. Zhang H, Gao Y, Jiang F, et al. Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146,958 pregnancies [published correction appears in Ultrasound Obstet Gynecol. 2015 Jul;46(1):130]. Ultrasound Obstet Gynecol. 2015;45(5):530-538.

128. Zhang S, Taylor AK, Huang X, Luo B, Spector EB, Fang P, et al. Venous thromboembolism laboratory testing (factor V Leiden and factor II c.*97G>A), 2018 update: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018 Dec;20(12):1489-1498.

Revision Details

Type of Revision	Summary of Changes	Date