

Guideline Number: CG043

Prenatal Testing

Summary

Oscar members who are pregnant may be eligible for prenatal testing to provide information about the health of both the mother and the baby. Prenatal testing can be performed invasively or noninvasively to look for a variety of birth defects and genetic conditions. Invasive testing includes several more involved procedures such as directly sampling the fluid or tissue surrounding the baby. Non-invasive testing is performed with simple blood tests. These tests can be performed at different stages of the pregnancy depending on the conditions being tested for. When clinical criteria are met, screening or diagnostic testing for fetal genetic disorders may be appropriate, regardless of maternal age. Additionally, high risk women, such as those over 35 years of age or with certain medical problems, are eligible for coverage of more advanced testing.

This guideline provides coverage criteria for prenatal tests and procedures. For a list of non-covered genetic tests, please refer to Oscar Clinical Guideline: Non-Covered Experimental, Investigational, and Unproven Services (CG012).

Definitions

“Invasive Prenatal Testing” includes procedures such as amniocentesis and chorionic villus sampling, where the tissue or fluid surrounding the baby is directly sampled.

“Noninvasive Prenatal Testing (NIPT)” is a test where a small amount of the mother’s blood is drawn to look for fragments of fetal genetic material called cell-free DNA. These small fragments can be used to look for fetal trisomy syndromes and determine the sex of the baby. NIPT can be performed as early as 10 weeks of gestation.

“Nuchal Ultrasound” is a procedure where ultrasound is used to determine the fluid in the neck of the growing baby to determine risk of various conditions such as trisomy 21 or cardiac problems.

“Carrier Screening” refers to the genetic testing of certain rare, inheritable conditions such as cystic fibrosis or spinal muscular atrophy. These conditions are usually inherited in an autosomal recessive fashion, meaning that both the mother and the father need to have the mutation.

“Expanded Carrier Screening” refers to genetic screening for multiple disorders instead of screening targeted for at risk disorders.

“Trisomy” is a the genetic condition of having an extra chromosome. Where the normal human genome has 23 pairs of chromosomes, errors in reproductive division to create the egg or sperm can result in an extra chromosome being included. The most common trisomies are trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome).

“Aneuploidy” is a broad term used to define the presence of an abnormal number of chromosomes. This can include trisomy syndromes, or conditions such as Turner’s syndrome where there is a missing chromosome (sex-chromosome aneuploidy)

Covered Services and Clinical Indications

General Coverage Criteria for Genetic Testing

Oscar considers genetic testing medically necessary to establish a molecular diagnosis of an inheritable disease when **ALL** of the following are met:

1. The test is FDA-approved, and clinical studies have proven the test to be clinically beneficial; **and**
2. The member displays clinical features, or is at direct risk of inheriting the mutation in question (pre-symptomatic); **and**
3. The result of the test will directly impact the treatment being delivered to the member; **and**
4. After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain; **and**
5. Testing is accompanied by genetic counseling and documented by a licensed genetic counselor.

Non-Invasive Prenatal Cell-Free DNA testing

Oscar covers non-invasive prenatal cell-free DNA testing when ALL of the following criteria are met:

1. The test is used to screen for trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) or trisomy 13 (Patau syndrome); **and**
2. The member has a confirmed single pregnancy; **and**
3. Any ONE of the following situations are present:
 - a. Maternal age will be at least 35 years old at the time of delivery; **or**
 - b. Fetal ultrasound has findings that indicate or are suspicious for aneuploidy; **or**
 - c. The member has history of prior pregnancy with one of the above trisomies; **or**
 - d. The first or second trimester screening tests for aneuploidy were positive; **or**

- e. There is a parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or 21; *and*
4. The member has not previously had NIPT for this pregnancy; *and*
5. The NIPT test has been approved by the FDA.

Standard CFTR (cystic fibrosis transmembrane conductance regulator) Mutation Panel

Oscar covers carrier screening for cystic fibrosis with the ACMG (American College of Medical Genetics) standard CFTR (cystic fibrosis transmembrane conductance regulator) mutation panel when ANY of the following criteria are met:

1. Couples seeking prenatal care; *or*
2. Couples planning a pregnancy; *or*
3. Members with a family history of cystic fibrosis; *or*
4. Members with a 1st degree relative identified as a cystic fibrosis carrier; *or*
5. Members with a partner who has cystic fibrosis or is a cystic fibrosis carrier; *or*
6. When the newborn screen is positive for CF *and* the sweat chloride test is inconclusive, intermediate or cannot be performed.

V Leiden Testing

Oscar covers factor V leiden genetic testing in pregnant members or those planning pregnancy when ALL of the following criteria are met:

1. Abnormal activated protein C (APC) resistance assay test; *and*
2. One of the following situations are met:
 - a. Venous thromboembolism (VTE) during the current or past pregnancy, or in the 6 weeks following a prior pregnancy; *or*
 - b. First degree blood relative with history of high-risk thrombophilia (e.g. antithrombin deficiency, factor V leiden mutation, or prothrombin G20210A mutation); *or*
 - c. First-degree blood relative with history of venous thromboembolism prior the age of 50 years old; *or*
 - d. Personal history of unprovoked VTE; *or*
 - e. Personal history of VTE associated with use of oral contraceptives or hormone therapy

Prothrombin G20210A Thrombophilia (F2 Gene) Testing

Oscar covers prothrombin G20210A thrombophilia (F2 Gene) testing in pregnant members or those planning pregnancy when ONE of the following criteria are met:

1. Venous thromboembolism (VTE) during the current or past pregnancy, or in the 6 weeks following a prior pregnancy; *or*
2. First degree blood relative with history of high-risk thrombophilia (e.g. antithrombin deficiency, factor V leiden mutation, or prothrombin G20210A mutation); *or*
3. First-degree blood relative with history of venous thromboembolism prior the age of 50 years old; *or*
4. Personal history of unprovoked VTE; *or*
5. Personal history of VTE associated with use of oral contraceptives or hormone therapy

Hemoglobinopathy and Thalassemia Testing

Oscar covers genetic testing for hemoglobinopathies and thalassemias (includes, but not limited to: Sickle Cell Anemia [HBB Gene], Alpha Thalassemia [HBA1/HBA2 Genes] and Beta Thalassemia [HBB Gene]) for couples planning pregnancy or seeking prenatal care when ONE of the following criteria are met:

1. Family history of a hemoglobinopathy; *or*
2. Family member who is affected or is a carrier with a known mutation; *or*
3. Suspected hemoglobinopathy based on results of a complete blood count (CBC) and hemoglobin analysis, such as low mean corpuscular hemoglobin or mean corpuscular volume; *or*
4. African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent

Spinal Muscular Atrophy Testing (SMN1 and SMN2)

Oscar covers spinal muscular atrophy genetic testing (SMN1 and SMN2) when ONE of the following criteria is met:

1. Carrier screening for couples seeking prenatal care or planning pregnancy; *or*
2. In the fetus or as a pre-implantation test when both parents are known carriers of the mutation

Fragile X Testing (FMRI gene)

Oscar covers fragile X testing (FMRI gene) in pregnant members or those planning pregnancy when ONE of the following criteria are met:

1. A family history of fragile X syndrome, *or*
2. A family history of unexplained developmental delay/intellectual disability, autism or primary ovarian insufficiency (POI); *or*
3. Fetuses of known carrier mothers

Tay-Sachs Disease Testing (HEXA gene)

Oscar covers Tay-Sachs disease testing (HEXA gene) in pregnant members or those planning pregnancy when ONE of the following criteria are met:

1. The member has an abnormal or inconclusive beta-hexosaminidase A enzyme activity; *or*
2. The member has an affected or carrier family member in whom a mutation has been identified;
or
3. The member or member's partner is of Ashkenazi Jewish, French Canadian, or Cajun descent; *or*
4. The member or member's partner is affected with or carrier of Tay-Sachs disease

Down Syndrome Testing

Oscar covers the following non-invasive testing options for Down syndrome in pregnant women wishing to undergo testing that have been adequately counseled:

- Preferred test: Second trimester quadruple screen, consisting of the following biomarkers:
 - Dimeric inhibin A *and*
 - Human chorionic gonadotropin (hCG) *and*
 - Maternal serum alpha-fetoprotein (MSAFP) *and*
 - Unconjugated estriol
- First trimester combined test, consisting of the following tests, to be used when earlier identification of aneuploidy is desired:
 - Nuchal translucency *and*
 - PAPP-A and beta-HCG
- When nuchal translucency is not available or the results are indeterminate, serum analyte combined test consisting of the following is warranted:
 - First trimester PAPP-A and beta-HCG *and*
 - Second trimester quadruple screen
- Full integrated testing, as defined by combination of the following:
 - First trimester combined test *and*
 - Second trimester quadruple screen
- Stepwise sequential testing, as defined by:
 - Initial first trimester combined test, followed by risk stratification, and if necessary, second trimester quadruple screen
- For high risk women meeting the criteria defined in the appropriate section above, NIPT may be appropriate to screen for Down syndrome

In addition to the above covered carrier screens and genetic tests, Oscar covers genetic testing of the diseases listed in Table 1 when ANY of the following criteria are met:

1. Genetic testing for a known familial variant mutation when it has been identified in the member, the member’s partner, or a blood relative; *or*
2. Targeted mutation analysis when ONE of the following criteria is met:
 - a. The member or reproductive partner is a known carrier of a disease-causing recessively inherited mutation; *or*
 - b. A disease-causing recessively inherited mutation has been identified in a blood relative and the relative has not had testing or is unavailable for genetic testing; *or*
3. Gene sequencing and/or gene duplication/deletion analysis when ONE of the following criteria is met:
 - a. The member meets criteria for target mutation analysis above; *or*
 - b. Targeted mutation analysis is not available or was previously negative

Table 1: Genetic diseases

Nuclear mitochondrial genes	Muscular dystrophies	Alpha and beta thalassemia
Long QT syndrome	DFNB1 non-syndromic hearing loss and deafness	21-hydroxylase deficiency
Retinoblastoma		Niemann-Pick disease
Gaucher disease	Rett syndrome	Von Hippel-Lindau disease
PTEN-related disorders	Canavan disease	Huntington disease

Expanded Carrier Screening Panels

Expanded carrier screening may be considered medically necessary when the indication and testing performed are consistent with the criteria set forth by the American Congress of Obstetricians and Gynecologists Committee on Genetics:

- The carrier frequency is greater than 1 in 100; *and*
- The phenotype is well-defined; *and*
- The condition will have a detrimental effect on quality of life; *and*
- The condition will cause cognitive and/or physical impairment; *and*
- The condition may require medical or surgical intervention; *and*
- The condition can be diagnosed prenatally; *and*
- The condition may be amenable to antenatal intervention to improve perinatal outcomes and may change delivery management.
- The condition is associated with early onset in life and not adult onset⁴⁹.

Chorionic Villus Sampling or Amniocentesis

For women with a major fetal structural abnormality detected on ultrasound examination and when MCG criteria are met, chorionic villus sampling or amniocentesis with chromosomal microarray are covered.

Coverage Exclusions

Non-Invasive Prenatal Cell-Free DNA testing

Non-invasive prenatal cell-free DNA testing is considered experimental, investigational, or unproven and thus not medically necessary for the following indications:

- Screening in women with average or low-risk pregnancies (as defined as not meeting high-risk criteria above):
 - *Rationale for non-coverage:* The use of NIPT cell-free DNA testing in women not meeting high risk criteria is currently not endorsed by the ACOG, ACMG, or other professional societies due to concerns over the small patient populations that have been studied, lack of appropriately powered studies, the methods used in such studies, and cost-effectiveness in this population.^{4,37}
- Multiple gestation pregnancy
 - *Rationale for non-coverage:* The use of NIPT cell-free DNA testing in multiple gestations is not endorsed by the ACOG, ACMG, or other professional societies due to lack of testing in this population and concerns over a higher rate of false negatives given the potential for variable amounts of cell-free DNA from each twin.^{10,17,33}
- Screening for sex-chromosome aneuploidy
 - *Rationale for non-coverage:* Higher failure rates, lower detection rates, more false positives, further research required and in line with the professional society guidelines. There have been some studies that have demonstrated potential efficacy for this indication but further research is required.¹⁴
- Vanishing twin syndrome or demised twin
 - *Rationale for non-coverage:* There are increased rates of false positives in cases of vanishing or demised twin in cases where the twin was aneuploid.¹²
- Screening for trisomy of chromosome: 7, 9, 16, or 22
 - *Rationale for non-coverage:* Evaluation for rare trisomies has not been fully explored in the literature, therefore the diagnostic utility of cell-free DNA testing in this setting has not yet been adopted by expert consensus guidelines.⁴
- Screening for microdeletions
 - cfDNA screening tests for microdeletions have not been validated clinically and are not recommended at this time (ACOG, 2016).^{4,41-42}

- Whole genome NIPT
 - *Rationale for non-coverage:* The outcomes and clinical utility of whole genome sequencing has not been validated in the scientific literature. Further research is required prior to guide clinical use.²⁹
- When used to determine the etiology of recurrent miscarriage
 - *Rationale for non-coverage:* The outcomes and clinical utility of cell-free DNA testing have not been validated in the scientific literature for evaluation of recurrent miscarriage. Further research is required prior to guide clinical use.
- When used to determine fetal sex
 - *Rationale for non-coverage:* While NIPT has been demonstrated the potential for determining fetal sex, the clinical outcomes and medical necessity of this indication have not been validated in the literature and using NIPT to determine fetal sex has not received formal guidance from the expert societies.⁴
- Fetal rhesus D (RhD) genotyping
 - *Rationale for non-coverage:* NIPT has seen some adoption across Europe in prenatal determination of Rhesus D genotyping, however, has not yet demonstrated improvement in clinical outcomes across large, validated studies. The ACOG and SMFM currently do not mention rhesus D genotyping as an indication for NIPT cfDNA testing.^{4, 3, 15}
- Cystic hygroma
 - *Rationale for non-coverage:* Cystic hygroma is considered a high-risk condition for fetal aneuploidy and thus direct consideration for invasive testing should be the next step. ACOG guidelines for cell-free DNA testing state, "If a fetal structural anomaly is identified on ultrasound examination, diagnostic testing should be offered rather than cell-free DNA screening".⁴

The following tests and biomarkers for the non-invasive screening for Down syndrome and other prenatal conditions are considered experimental, investigational, or unproven and thus not medically necessary unless performed as

- Second trimester screening with:
 - Beta subunit of hCG
 - Human placental lactogen
 - Pregnancy-associated plasma protein A (PAPP-A)
 - Urinary beta-core
 - *Rationale for non-coverage:* The clinical efficacy of diagnosing trisomy syndromes with with these biomarkers has been evaluated primarily for first trimester pregnancies and

has not been established for use in the second trimester and may be inferior to first trimester use.^{4, 40}

- A Disintegrin Metalloprotease 12 (ADAM12)
 - *Rationale for non-coverage:* Laigaard et al (2007) looked at the use of ADAM12 as a first trimester screen for Down syndrome and found reduced levels of the biomarker, however stated that further research was needed to define its role in the screening process. A second study by Christiansen et al (2007) came to the same conclusions for ADAM12 use in the second trimester. ACOG and other societies do not currently mention the use of this biomarker.^{4, 15, 19}
- Placental protein 13 (PP13)
 - *Rationale for non-coverage:* Koster et al (2009) looked at the use of PP13 as a first trimester screen for Down syndrome and other common trisomies. They found non-significant differences in Down syndrome and variable decreases of the biomarker in other trisomies, and concluded that PP13 was NOT a good marker for Down Syndrome screening.¹⁸
- First-trimester NT measurement alone (without first-trimester serum analyte testing) in the absence of fetal cystic hygroma in singleton pregnancies
 - *Rationale for non-coverage:* Nuchal translucency testing alone is not recommended by any of the expert consensus guidelines from ACOG or other speciality-specific societies. Research has shown that adding biomarker testing to the ultrasound decreases the rate of fetal karyotyping required and improves the predictive value.²³
- First-trimester serum analyte testing (hCG* and PAPP-A) alone without NT measurement
 - *Rationale for non-coverage:* First trimester biomarker testing alone is not recommended by any of the expert consensus guidelines from ACOG or other speciality-specific societies. The FASTER and SURUSS studies have shown that combining first trimester screening with nuchal translucency or with second trimester quadruple screen increases the detection rate and decreases false positives.²⁴
- First-trimester ultrasound assessment of the nasal bone
 - *Rationale for non-coverage:* A large study of 1027 patients by Orlandi et al (2003) looked at ultrasound of the nasal bone as a marker for Down syndrome. While they noted that its inclusion in first trimester screening might have some utility, they concluded that "Large datasets are needed to confirm whether the measurement of nasal bone length provides additional benefits beyond the assessment of the presence or absence of the nasal bone."³⁰
- Any other biomarker not defined above, including but not limited to the following, is considered investigational, experimental, and/or not medically necessary for use in prenatal screening:

- o First-trimester maternal serum anti-Mullerian hormone level
- o First-trimester maternal serum placental growth factor level
- o Maternal plasma microRNA
- o First-trimester maternal plasma levels of follistatin-related gene protein
- Ultrasound evaluation of the right subclavian artery (RSA)
 - o *Rationale for non-coverage:* A 2008 study by Zalel et al. looked at the utility of aberrant subclavian artery with ultrasound as a marker of Down syndrome. They found that 37.5% of fetuses with Down Syndrome had an aberrant right subclavian artery, and 1.4% without Down syndrome. However, they concluded that “Larger prospective studies are needed to examine the significance of ARSA as an isolated finding and the potential of ARSA as a marker in Down syndrome screening.”⁴⁵

Prenatal lead level testing is considered experimental, investigational, and/or not medically necessary.

- *Rationale for non-coverage:* The Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists do not recommend blood lead testing of all pregnant women in the United States.¹

Benefit Details

Testing must be performed by an in-network provider when available.

NIPT is only considered medically necessary ONE time per pregnancy.

Coverage for expanded carrier screening is subject to review of medical necessity and current clinical evidence; coverage may be limited to risk-based conditions.

Applicable Lines of Business

This Clinical Guideline is applicable to all states and plan types. Please refer to the member Certification of Coverage and Schedule of Benefits for coverage details.

Applicable Billing Codes (HCPCS/CPT Codes)

CPT/HCPCS Codes covered if criteria are met:	
Code	Description
0009M	Fetal aneuploidy (trisomy 21, and 18) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each

	trisomy
59015	Chorionic villus sampling, any method
76813	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation
81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
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 methylation status)
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for 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
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
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)0
81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
81400	Molecular pathology procedure, Level 1 straight chain, MCAD)
81401	Molecular pathology procedure, Level 2
81403	Molecular pathology procedure, Level 4
81404	Molecular pathology procedure, Level 5
81405	Molecular pathology procedure, Level 6
81406	Molecular pathology procedure, Level 7
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
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

81508	Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
81509	Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score
81510	Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
81511	Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)
81512	Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score
82105	Alpha-fetoprotein (AFP); serum
82667	Estriol
84163	Pregnancy-associated plasma protein-A (PAPP-A)
86336	Inhibin A
88235	Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
88291	Cytogenetics and molecular cytogenetics, interpretation and report
S3618	Blood chemistry for free beta human chorionic gonadotropin (HCG)
ICD-10 codes covered if criteria are met:	
<i>Code</i>	<i>Description</i>
O09.00 - O09.899	Supervision of high risk pregnancy
O28.1	Abnormal biochemical finding on antenatal screening of mother [fetal ultrasonographic findings predicting an increased risk of fetal aneuploidy or positive screening test for an aneuploidy]

O28.5	Abnormal chromosomal and genetic finding on antenatal screening of mother [fetal ultrasonographic findings predicting an increased risk of fetal aneuploidy or positive screening test for an aneuploidy]
Z14.1	Cystic fibrosis carrier
Z14.01 - Z14.02	Hemophilia A carrier
Z14.8	Genetic carrier of other disease
Z34.00 - Z34.93	Encounter for supervision of normal pregnancy
Z36	Encounter for antenatal screening of mother
Z84.81	Family history of carrier of genetic disease
Additional ICD-10 codes covered if criteria are met for prothrombin G20210A thrombophilia (F2 Gene) or V leiden genetic testing	
<i>Code</i>	<i>Description</i>
O22.30 - O22.33	Deep phlebothrombosis in pregnancy
Z86.718	Personal history of other venous thrombosis and embolism
ICD-10 codes not covered:	
<i>Code</i>	<i>Description</i>
O30.00 - O30.93	Multiple gestation
O31.00x0 - O31.8x99	Complications specific to multiple gestation
Q93.88	Other microdeletions

CPT/HCPCS codes not covered for indications listed in this guideline:	
<i>Code</i>	<i>Description</i>
76815	Ultrasound, pregnant uterus, real time with image documentation, limited (e.g., fetal heart beat, placental location, fetal position and/or qualitative amniotic

	fluid volume), 1 or more fetuses [when used for ultrasound assessment of nasal bone translucency]
81508	Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score [in second trimester]
81509	Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score [in second trimester]
82397	Chemiluminescent assay [when used for anti-Mullerian hormone level]
83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method [not covered for prenatal genetic testing]
83520	Immunoassay, analyte, quantitative; not otherwise specified [not covered for prenatal genetic testing]
83632	Lactogen, human placental (HPL) human chorionic somatomammotropin [in second trimester]
84112	Evaluation of cervicovaginal fluid for specific amniotic fluid protein(s) (eg, placental alpha microglobulin-1 [PAMG-1], placental protein 12 [PP12], alpha-fetoprotein), qualitative, each specimen

CPT/HCPCS codes <i>never</i> covered:	
<i>Code</i>	<i>Description</i>
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
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal

	blood
--	-------

References

1. ACOG Committee Opinion: Lead Screening During Pregnancy and Lactation. August 2012, reaffirmed 2016. Available at <https://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Lead-Screening-During-Pregnancy-and-Lactation>. Accessed August 29, 2017.
2. Alamillo CM, Krantz D, Evans M, Fiddler M, Pergament E. Nearly a third of abnormalities found after first-trimester screening are different than expected: 10-year experience from a single center. *Prenat Diagn* 2013;33:251–6.
3. Allyse M, Minear MA, Berson E, et al. Non-invasive prenatal testing: a review of international implementation and challenges. *Int J Womens Health*. 2015;7:113-26.
4. American College of Obstetricians and Gynecologists Committee on Genetics. Committee Opinion No. 545: Noninvasive prenatal testing for fetal aneuploidy. *Obstet Gynecol*. 2012 Dec;120(6):1532-4.
5. Ashoor G, Syngelaki A, Poon LC, Rezende JC, Nicolaidis KH. Fetal fraction in maternal plasma cell-free DNA at 11-13 weeks' gestation: relation to maternal and fetal characteristics. *Ultrasound Obstet Gynecol* 2013;41:26–32.
6. Ashoor G, Syngelaki A, Wagner M, et al. Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18. *Am J Obstet Gynecol* 2012;206(4):322.e1–5.
7. Bianchi DW, Parker RL, Wentworth J, Madankumar R, Saffer C, Das AF, et al. DNA sequencing versus standard prenatal aneuploidy screening. CARE Study Group. *N Engl J Med* 2014;370:799–808.
8. Bianchi DW, Parsa S, Bhatt S, Halks-Miller M, Kurtzman K, Sehnert AJ, et al. Fetal sex chromosome testing by maternal plasma DNA sequencing: clinical laboratory experience and biology. *Obstet Gynecol* 2015;125:375–82.
9. Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ, Rava RP. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. MatErnal BLOOD IS Source to Accurately diagnose fetal aneuploidy (MELISSA) Study Group [published erratum appears in *Obstet Gynecol* 2012;120:957]. *Obstet Gynecol* 2012;119:890–901.
10. 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;32:730–4.

11. Christiansen M, Spencer K, Laigaard J, et al. ADAM 12 as a second-trimester maternal serum marker in screening for Down syndrome. *Prenat Diagn.* 2007;27(7):611-615.
12. Curnow KJ, Wilkins-Haug L, Ryan A, Kirkizlar E, Stosic M, Hall MP, et al. Detection of triploid, molar, and vanishing twin pregnancies by a single-nucleotide polymorphism-based noninvasive prenatal test. *Am J Obstet Gynecol* 2015;212:79.e1–79.e9.
13. Dar P, Curnow KJ, Gross SJ, Hall MP, Stosic M, Demko Z, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. *Am J Obstet Gynecol* 2014;211:527.e1–527.e17.
14. 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;45:249–66.
15. Goodspeed TA, Allyse M, Sayres LC, Norton ME, Cho MK. Translating cell-free fetal DNA technology: structural lessons from non-invasive RhD blood typing. *Trends Biotechnol.* 2013;31(1):7-9.
16. 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;15:395–8.
17. Huang X, Zheng J, Chen M, Zhao Y, Zhang C, Liu L, et al. Noninvasive prenatal testing of trisomies 21 and 18 by massively parallel sequencing of maternal plasma DNA in twin pregnancies. *Prenat Diagn* 2014;34:335–40.
18. Koster MP, Wortelboer EJ, Cuckle HS, et al. Placental protein 13 as a first trimester screening marker for aneuploidy. *Prenat Diagn.* 2009;29(13):1237-1241.
19. Laigaard J, Cuckle H, Wewer UM, Christiansen M. Maternal serum ADAM12 levels in Down and Edwards' syndrome pregnancies at 9-12 weeks' gestation. *Prenat Diagn.* 2006;26(8):689-691.
20. Lo YM, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, et al. Presence of fetal DNA in maternal plasma and serum. *Lancet* 1997;350:485–7.
21. Lo YM, Zhang J, Leung TN, Lau TK, Chang AM, Hjelm NM. Rapid clearance of fetal DNA from maternal plasma. *Am J Hum Genet* 1999;64:218–24.
22. Malone FD, Canick JA, Ball RH, et al. 2005. First-trimester or second-trimester screening, or both, for Down's syndrome. *N. Engl. J. Med.* 353:2001–11
23. Marsk A, Grunewald C, Saltvedt S, Valentin L, Almström H. If nuchal translucency screening is combined with first-trimester serum screening the need for fetal karyotyping decreases. *Acta Obstet Gynecol Scand.* 2006;85(5):534-8.
24. Messerlian, GM. Down syndrome: Overview of prenatal screening. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com> (Accessed on August 28, 2017.)

25. Nicolaidis 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;207:374.e1–374.e6.
26. 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;207:137.e1–137.e8.
27. 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;372:1589–97.
28. Norton ME, Jelliffe-Pawłowski LL, Currier RJ. Chromosome abnormalities detected by current prenatal screening and noninvasive prenatal testing. *Obstet Gynecol* 2014;124:979–86.
29. Norton ME. Noninvasive prenatal testing to analyze the fetal genome. *Proc Natl Acad Sci USA*. 2016;113(50):14173-14175.
30. Orlandi F, Bilardo CM, Campogrande M, et al. Measurement of nasal bone length at 11-14 weeks of pregnancy and its potential role in Down syndrome risk assessment. *Ultrasound Obstet Gynecol*. 2003;22(1):36-9.
31. 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;14:296–305.
32. Palomaki GE, Kloza EM, Lambert-Messerlian GM, Haddow JE, Neveux LM, Ehrich M, et al. DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. *Genet Med* 2011;13:913–20.
33. Palomaki, G. Prenatal screening for common aneuploidies using cell-free DNA. UpToDate. Waltham, MA: UpToDate Inc. <http://www.uptodate.com> (Accessed on August 28, 2017.)
34. Pergament E, Cuckle H, Zimmermann B, Banjevic M, Sigurjonsson S, Ryan A, et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. *Obstet Gynecol* 2014;124:210–8.
35. Porreco RP, Garite TJ, Maurel K, Marusiak B, Ehrich M, van den Boom D, et al. Noninvasive prenatal screening for fetal trisomies 21, 18, 13 and the common sex chromosome aneuploidies from maternal blood using massively parallel genomic sequencing of DNA. Obstetrix Collaborative Research Network. *Am J Obstet Gynecol* 2014;211:365.e1–365.12.
36. Position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. Benn P, Borell A, Chiu R, et al. *Prenat Diagn*. 2013 Jul;33(7):622-9.
37. SMFM Statement: Maternal serum cell-free DNA screening in low risk women. SMFM publications and guidelines. Available at <https://www.smfm.org/publications/157-smfm->

statement-maternal-serum-cell-free-dna-screening-in-low-risk-women. Accessed August 29, 2017.

38. Sparks AB, Struble CA, Wang ET, Song K, Oliphant A. Noninvasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18. *Am J Obstet Gynecol* 2012;206:319.e1–319.e9.
39. Sparks AB, Wang ET, Struble CA, Barrett W, Stokowski R, McBride C, et al. Selective analysis of cell-free DNA in maternal blood for evaluation of fetal trisomy. *Prenat Diagn* 2012;32:3–9.
40. Spencer K, Crossley JA, Green K, Worthington DJ, Brownbill K, Aitken DA. Second trimester levels of pregnancy associated plasma protein-A in cases of trisomy 18. *Prenat Diagn*. 1999;19(12):1127-34.
41. 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;92:167–76.
42. Wapner RJ, Babiarez JE, Levy B, Stosic M, Zimmermann B, Sigurjonsson S, et al. Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes. *Am J Obstet Gynecol* 2015;212:332.e1–332.e9.
43. Willems PJ, Dierickx H, Vandenakker E, Bekedam D, Segers N, Deboulle K, et al. The first 3,000 Non-Invasive Prenatal Tests (NIPT) with the Harmony test in Belgium and the Netherlands. *Facts Views Vis Obgyn* 2014;6:7–12.
44. Wilson KL, Czerwinski JL, Hoskovec JM, et al. NSGC practice guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy. *J Genet Couns*. 2013 Feb;22(1):4-15. doi: 10.1007/s10897-012-9545-3. Epub 2012 Nov 22.
45. Zalel Y, Achiron R, Yagel S, Kivilevitch Z. Fetal aberrant right subclavian artery in normal and Down syndrome fetuses. *Ultrasound Obstet Gynecol*. 2008;31(1):25-9.
46. Zhang H, Gao Y, Jiang F, Fu M, Yuan Y, Guo Y, et al. Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146 958 pregnancies. *Ultrasound Obstet Gynecol* 2015;45:530–8.
47. Zimmermann B, Hill M, Gemelos G, Demko Z, Banjevic M, Baner J, et al. Noninvasive prenatal aneuploidy testing of chromosomes 13, 18, 21, X, and Y, using targeted sequencing of polymorphic loci. *Prenat Diagn* 2012;32:1233–41.
48. ACOG Committee Opinion: Carrier Screening for Genetic Conditions. March 2017. Available at <https://www.acog.org/-/media/Committee-Opinions/Committee-on-Genetics/co691.pdf?dmc=1&ts=20170309T1313372850>. Accessed October 6, 2017.
49. ACOG Committee Opinion: Carrier Screening in the Age of Genomic Medicine. March 2017. Available at <https://www.acog.org/-/media/Committee-Opinions/Committee-on-Genetics/co690.pdf?dmc=1&ts=20170718T0046152351>. Accessed October 6, 2017.

Clinical Guideline Revision / History Information

Original: Review/Revise Dates	Approval Signature/ Title
Original Date: Reviewed/Revised: Signed:	10/11/2017 Sean Martin, MD, Medical Director

Oscar may utilize evidenced-based guidelines (e.g., MCG, U.S. Food and Drug Administration) to establish its medical necessity coverage criteria. These criteria have been carefully researched and are updated at least annually to be consistent with current evidence-based criteria. Oscar may delegate utilization review of certain services to third-party utilization review agents. Oscar's clinical guidelines are utilized only for utilization management decisions made directly by Oscar.

The services described in this guideline are subject to the terms, conditions and limitations of the Member's Certificate of Coverage and Schedule of Benefits. Oscar may modify guideline without prior written notice unless otherwise required by Oscar's administrative procedures, applicable state law, or applicable federal law. If there is a difference between a guideline and the Member's Certificate of Coverage, the Certificate of Coverage will govern conditions of coverage. If there is a difference between a guideline and applicable state or federal laws, the applicable laws will take precedence.