**03-59000-18**

**Original Effective Date: 03/15/13**

**Reviewed: 06/26/25**

**Revised: 07/15/25**

# Subject: Noninvasive Prenatal Screening Using Cell-Free Fetal DNA

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**


| | | | | | |
|---|---|---|---|---|---|
| Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions | Related Guidelines |
| Other | References | Updates | | | |


## DESCRIPTION:

National guidelines recommend that all pregnant individuals be offered screening for fetal chromosomal abnormalities, most of which are aneuploidies, an abnormal number of chromosomes. Trisomy syndromes are aneuploidies involving 3 copies of 1 chromosome. Trisomies 21, 18, and 13 are the most common forms of fetal aneuploidy that survive to birth. There are numerous limitations to standard screening for these disorders using maternal serum and fetal ultrasound. Noninvasive prenatal screening (NIPS) analyzing fetal cell-free DNA (cfDNA) in maternal serum is a potential complement or alternative to conventional serum screening. NIPS using fetal cfDNA has also been proposed to screen for microdeletions. Prenatal testing for twin zygosity using fetalcfDNA has been proposed to inform decisions about early surveillance for twin-twin transfusion syndrome and other monochorionic twin-related abnormalties.

The technology for noninvasive, sequencing-based testing of maternal serum for fetal trisomy syndromes involves detection of fetal cfDNA fragments present in the plasma of pregnant individuals. As early as 8 to 10 weeks of gestation, these fetal DNA fragments comprise 6% to 10% or more of the total fetal cfDNA in a maternal plasma sample. The tests are unable to provide a result if the fetal fraction is too low (ie, <4%). Fetal fraction can be affected by maternal and fetal characteristics.

Moise (2025) states RhD-negative patients who give birth to a RhD-positive newborn or who are otherwise exposed to RhD-positive red blood cells (RBCs) are at risk of developing anti-D antibodies. The RhD-positive fetuses/neonates of these mothers are at risk of developing hemolytic disease of the fetus and newborn (HDFN), which can be associated with serious morbidity or mortality. Dukhovny (2025) concludes RhD is an autosomal-dominant trait, rather than a disorder. Use of cfDNA after 10 weeks of gestation to determine fetal RHD status has significant clinical utility. For example, in an alloimmunized

pregnancy, if the fetus is RHD positive, monitoring maternal anti-D titers is appropriate because of the risk for hemolytic disease of the fetus and newborn. If the fetus is RHD negative, the fetus is not at risk, so such monitoring can be avoided. This strategy essentially eliminates the need for amniocentesis to determine fetal RHD status.

A newer approach to cell free DNA testing called the Vanadis NIPT (noninvasive prenatal testing) does not involve polymerase chain reaction (PCR) amplification or sequencing. The procedure consists of digestion of cell-free DNA (cfDNA) using a restriction enzyme. The digested cfDNA is then hybridized and ligated to chromosome specific DNA probes forming a circular DNA. All non-circular DNA is removed by exonuclease treatment. Finally, the circular DNA containing the cfDNA is amplified with rolling circle amplification to form rolling circle products that are labeled with chromosome- specific fluorescently labeled DNA probes. The fluorescently labeled rolling circle productss are imaged and counted with an automated microscopy scanner. The microscope takes multiple images from each well with different spectral filters, i.e each wavelength range presents a specific chromosome. With image analysis algorithms, the fluorescently labeled rolling circle products are counted for each sample. The ratio between the number of chromosome-specific rolling circle products is then transferred to risk calculation software to calculate the likelihood of a trisomy. Currently, Vanadis NIPT provides results for trisomy 21, trisomy 18 and trisomy 13, and fetal sex determination.

Single-gene disorders (also known as monogenic disorders) are caused by a variation in a single gene. Individually, single-gene disordersare rare, but collectively are present in approximately 1% of births. The Vistara Single-Gene Disorder Test panel screens for 25 conditions that result from variants across 30 genes. These include Noonan syndrome and other Noonan spectrum disorders, skeletal disorders (e.g., Osteogenesis Imperfecta, achondroplasia), craniosynostosis syndromes,Cornelia de Lange syndrome, Alagille syndrome, tuberous sclerosis, epileptic encephalopathy,SYNGAP1-related intellectual disability,CHARGE syndrome, Sotos syndrome, and Rett syndrome. The clinical presentation and severity of these disorders can vary widely. Some, but not all, can be detected by prenatal ultrasound examination.

**Summary and Analysis of Evidence**: Individuals with singleton or twin pregnancy who receive NIPS for T21, T18, and T13 using fetal cfDNA, the evidence includes observational studies and systematic reviews. Published studies on available tests and meta-analyses of these studies have consistently demonstrated very high sensitivity and specificity for detecting Down syndrome (T21) in singleton pregnancies. Most studies included only individuals at high-risk of T21, but several studies have reported similar levels of diagnostic accuracy in average-risk individuals. Compared with standard serum screening, both the sensitivity and specificity of fetal cfDNA screening are considerably higher. As a result, screening with fetal cfDNA for T21 will result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures. Screening for T18 and T13 along with T21 may allow for preparation for fetal demise or termination of the pregnancy prior to fetal loss. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. The evidence for NIPS for sex chromosome aneuploidies using fetal cfDNA includes observational studies, mainly in high-risk pregnancies, and systematic reviews. Meta-analyses of available data have suggested high sensitivities and specificities, but the small number of cases makes definitive conclusions difficult. In addition, the clinical utility of identifying sex chromosome aneuploidies during pregnancy is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. NIPS for T21, T18, and T13 using Vanadis NIPT, the evidence

includes 2 industry sponsored studies. The available studies on clinical validity have limitations, and the added benefit of Vanadis NIPT compared with current approaches is unclear. Moreover, the clinical utility of Vanadis NIPT remains unclear and has not been evaluated in published studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. The evidence for NIPS for single-gene disorders includes validation studies and a case study. There is insufficient evidence on clinical validity and data demonstrating improvement are unavailable. The American College of Obstetricians and Gynecologists (ACOG) Practice Advisory Cell-free DNA to Screen for Single-Gene Disorders (2019, reaffirmed 2023) concluded, "Although this technology is available clinically and marketed as a single-gene disorder prenatal screening option for obstetric care providers to consider in their practice, often in presence of advanced paternal age, there has not been sufficient data to provide information regarding accuracy and positive and negative predictive value in the general population. For this reason, single-gene cell-free DNA screening is not currently recommended in pregnancy." The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## POSITION STATEMENT:

**NOTE:** Coverage for genetic testing, screening, and counseling are applicable only under those contracts that include benefits for genetic testing, preventive health services, screening services, and medical counseling.

Noninvasive prenatal testing (NIPT) using cfDNA to screen for trisomy 21, 18, 13 **meets the definition of medical necessity** in members with singleton or twin pregnancies.

NIPT using cfDNA for fetal RhD genotyping **meets the definition of medical necessity** in known RhD negative members when amniocentesis is declined or contraindicated.

NIPT using cfDNA is considered **experimental or investigational** for all other indications, including:

- fetal sex chromosome aneuploidies
- microdeletions
- to screen for single-gene disorders (e.g. Vistara™ NIPT).

The evidence is insufficient to determine the effects of the technology on health outcomes.

Vanadis® NIPT of maternal plasma to screen for trisomy 21, 18 and 13 is considered **experimental or investigational** in all situations. The evidence is insufficient to determine the effects of the technology on health outcomes.

## BILLING/CODING INFORMATION:

### CPT Coding:

| | |
|---|---|
| 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 |

| | |
|---|---|
| 81422 | Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood **(Investigational)** |
| 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 (Harmony™ Prenatal Test) |
| 0060U | Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood (**Investigational**) |
| 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 |
| 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 (**Investigational**) |
| 0494U | Red blood cell antigen (fetal RhD gene analysis), next-generation sequencing of circulating cell-free DNA (cfDNA) of blood in pregnant individuals known to be RhD negative, reported as positive or negative [Rh Test, Natera™] |

### ICD-10 Diagnosis Codes That Support Medical Necessity:

| | |
|---|---|
| O09.511 | Supervision of elderly primigravida, first trimester |
| O09.512 | Supervision of elderly primigravida, second trimester |
| O09.521 | Supervision of elderly multigravida, first trimester |
| O09.522 | Supervision of elderly multigravida, second trimester |
| O30.001 – O30.099 | Twin pregnancy |
| Z31.430 – Z31.438 | Encounter for genetic testing of female for procreative management |
| Z34.00 – Z34.93 | Encounter for supervision of normal pregnancy |
| Z36.0 – Z36.9 | Encounter for antenatal screening of mother |

## REIMBURSEMENT INFORMATION:

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Advantage Products:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline reviewed date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

## DEFINITIONS:

No guideline specific definitions apply.

## RELATED GUIDELINES:

**Genetic Testing, 05-82000-28**

## OTHER:

**Commercial tests available (not all-inclusive):**

**Harmony®**: T21, T18, T13. (optional testing for sex chromosome abnormalities, microdeletions, fetal sex)
**InformaSeq®**: T21, T18, T13. (optional testing for sex chromosome abnormalities)
**MaterniT®21 PLUS**: T21, T18, T13, and fetal sex aneuploidies. (optional testing for microdeletions)
**Panorama™**: T21, T18, T13, and sex chromosome abnormalities. (optional testing for microdeletions)
**Prequel™**: T21, T18, T13, sex chromosome abnormalities, and microdeletions.
**QNatal® Advanced**: T21, T18, T13 and sex chromosome abnormalities. (optional testing for microdeletions)
**Vasistera™**: T21, T18, T13. (optional sex chromosome abnormalities, fetal sex)
**Veracity®**: T21, T18, T13, sex chromosome aneuploidies, and microdeletions.
**Verifi®**: T21, T18, T13. (optional testing for sex chromosome aneuploidies, microdeletions)
**VisibiliT**: T21, T18, fetal sex.

## REFERENCES:


1. American College of Obstetricians and Gynecologists (ACOG). ACOG Clinical Practice Update: Paternal and Fetal Genotyping in the Management of Alloimmunization in Pregnancy, 2024; accessed at acog.org.
2. American College of Obstetricians and Gynecologists (ACOG). ACOG Practice Advisory: Cell-free DNA to Screen for Single-Gene Disorders, 2019 (reaffirmed Sept. 2024); accessed at acog.org.
3. American College of Obstetricians and Gynecologists (ACOG). ACOG Practice Bulletin #226, Screening for Fetal Chromosomal Abnormalities, 2020; accessed at smfm.org.
4. Bai T, Liu S, et al. Performance of noninvasive prenatal screening in twin pregnancies: a retrospective study of 5469 twin pregnancies. J Matern Fetal Neonatal Med. 2021 Apr 1;1-9. PMID: 33792471.
5. Bassett AS, McDonald-McGinn DM, et al. Practical guidelines for managing patients with 22q11.2 deletion syndrome. J Pediatr. 2011 Aug;159(2):332-9.e1. doi: 10.1016/j.jpeds.2011.02.039.
6. Blue Cross Blue Shield Association Evidence Positioning System®. 4.01.21 Noninvasive Prenatal Screening for Fetal Aneuploidies, Microdeletions, and Twin Zygosity Using Cell-Free Fetal DNA, 04/25.
7. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Noninvasive maternal plasma sequencing-based screening for fetal aneuploidies other than trisomy 21. TEC Assessments 2014; Volume 29, Tab 7.
8. Blue Cross Blue Shield Association (BCBSA), Technology Evaluation Center (TEC). Sequencing-Based Tests to Determine Fetal Down Syndrome (Trisomy 21) from Maternal Plasma DNA, Volume 27, No. 10 April 2013.

9. Chen M, Jiang F, et al. Validation of fetal DNA fraction estimation and its application in noninvasive prenatal testing for aneuploidy detection in multiple pregnancies. Prenat Diagn. 2019 Dec;39(13):1273-1282. PMID: 31671222.
10. Cheung EN, George, SR, et al. Neonatal hypocalcemia, neonatal seizures, and intellectual disability in 22q11.2 deletion syndrome. Genet Med. 2014 Jan;16(1):40-4. doi: 10.1038/gim.2013.71.
11. Chibuk J, Rafalko J, et al. Cell-free DNA screening in twin pregnancies: A more accurate and reliable screening tool. Prenat Diagn. 2020 Sep;40(10):1321-1329.
12. Dar P, Jacobsson B, et al. Cell-free DNA screening for prenatal detection of 22q11.2 deletion syndrome. Am J Obstet Gynecol. 2022 Jul;227(1):79.e1-79.e11.
13. Dukhovny S. Cell-free DNA screening for fetal conditions other than the common aneuploidies, 2025. UpToDate, Wilkins-Haug L, Barss VA (Eds.), UpToDate, Waltham, MA; accessed at uptodate.com.
14. Dungan JS, Klugman S, et al. Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population: An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023 Feb;25(2):100336.
15. Dyr B, Boomer T, et al. A new era in aneuploidy screening: cfDNA testing in 30,000 multifetal gestations: Experience at one clinical laboratory. PloS ONE. 2019; 14(8): e0220979. PMID: 31393959.
16. Ericsson O, Ahola T, et al. Clinical validation of a novel automated cell-free DNA screening assay for trisomies 21, 13, and 18 in maternal plasma. Prenat Diagn. 2019;39(11):1011-1015. PMID: 31429096.
17. Gil MM, Galeva S, et al. Screening for trisomies by cfDNA testing of maternal blood in twin pregnancy: update of The Fetal Medicine Foundation results and meta-analysis. Ultrasound Obstet Gynecol. Jun 2019; 53(6): 734-742.
18. Gil MM, Quezada MS, Bregant B, et al, Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies. Ultrasound Obstet Gynecol. 2013 Jul;42(1):34-40.
19. Gilstrop Thompson M, Xu W, et al. Clinical Validation of a Prenatal Cell-Free DNA Screening Test for Fetal RHD in a Large U.S. Cohort. Obstet Gynecol. 2024 Nov 26;145(2):211–216. doi: 10.1097/AOG.0000000000005794.
20. Grand K, Levitt Katz LE, et al. The impact of hypocalcemia on full scale IQ in patients with 22q11.2 deletion syndrome. Am J Med Genet A. 2018 Oct;176(10):2167-2171. doi: 10.1002/ajmg.a.40535.
21. Gregg AR, Gross SJ, Best RG et al. ACMG statement on noninvasive prenatal screening for fetal aneuploidy. Genet Med 2013; 15(5):395-8.
22. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. Oct 2016;18(10):1056-1065.
23. Judah H, Gil MM, et al. Cell-free DNA testing of maternal blood in screening for trisomies in twin pregnancy: updated cohort study at 10-14 weeks and meta-analysis. Ultrasound Obstet Gynecol. 2021 Aug;58(2):178-189. PMID: 33838069.
24. Kypri E, Ioannides M, et al. Non-invasive prenatal testing of fetal chromosomal aneuploidies: validation and clinical performance of the veracity test. Mol Cytogenet. 2019; 12: 34. PMID: 31338126.
25. Mateus-Nino JF, Wynn J, et al. Clinical Performance of Cell-Free DNA for Fetal RhD Detection in RhD Negative Pregnant Individuals in the United States. Obstet Gynecol. 2025 Feb 27;145(4):402–408. doi: 10.1097/AOG.0000000000005850.
26. Mohan P, Lemoine J, et al. Clinical experience with non-invasive prenatal screening for single-gene disorders. UltrasoundObstet Gynecol. Jan 2022; 59(1):33-39.

27. Moise KJ. RhD alloimmunization: Prevention in pregnant and postpartum patients, 2025. UpToDate, Lockwood CJ, Barss VA (Eds.). UpToDate, Waltham, MA; accessed at uptodate.com.
28. Mortazavipour MM, Mahdian R, et al. The current applications of cell-free fetal DNA in prenatal diagnosis of single-gene diseases: A review. Int J Reprod Biomed. 2022 Sep 6;20(8):613-626.
29. Motevasselian M, Saleh Gargari S, et al. Non-invasive prenatal test to screen common trisomies in twin pregnancies. Mol Cytogenet. 2020; 13: 5. PMID: 32042312.
30. National Society of Genetic Counselors (NSGC), Noninvasive prenatal testing/ noninvasive prenatal diagnosis (NIPT/NIPD), accessed at nsgc.org.
31. Norwitz ER, McNeill G, et al. Validation of a Single-Nucleotide Polymorphism-Based Non-Invasive Prenatal Test in Twin Gestations: Determination of Zygosity, Individual Fetal Sex, and Fetal Aneuploidy. J Clin Med. 2019 Jun 28;8(7):937.
32. Palomaki GE, Messerlian GM, Halliday JV. Prenatal screening for common aneuploidies using cell-free DNA, 2025. In UpToDate, Wilkins-Haug L, Barss VA (Eds), UpToDate, Waltham, MA; accessed at uptodate.com.
33. Porreco RP, Garite TJ, Maurel K, 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. Am J Obstet Gynecol. Mar 19 2014.
34. Rego S, Ashimi Balogun O, et al. Cell-Free DNA Analysis for the Determination of Fetal Red Blood Cell Antigen Genotype in Individuals With Alloimmunized Pregnancies. Obstet Gynecol. 2024 Jul 25;144(4):436–443. doi: 10.1097/AOG.0000000000005692.
35. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. SMFM Statement: clarification of recommendations regarding cell-free DNA aneuploidy screening. Am J Obstet Gynecol. Dec 2015;213(6):753-754.
36. Tan Y, Gao Y, et al. Noninvasive prenatal testing (NIPT) in twin pregnancies with treatment of assisted reproductive techniques (ART) in a single center. Prenat Diagn. 2016 Jul;36(7):672-9. PMID: 27150972.
37. Taylor-Phillips S, Freeman K, Geppert J, et al. Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis. BMJ Open. 2016;6(1):e010002.

## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 06/26/25.

## GUIDELINE UPDATE INFORMATION:

| | |
|---|---|
| 03/15/13 | New Medical Coverae Guideline. |
| 07/01/13 | Quarterly HCPCS updates. Added code 0005M. Revised Program Exception section. |
| 10/15/13 | Revision; position statements and guideline title updated; formatting changes. |
| 01/01/14 | Annual HCPCS update. Added code 81507; deleted code 0005M. |
| 03/15/14 | Annual review; position statements maintained and references updated. |
| 01/01/15 | Annual HCPCS/CPT update. Added code 81420. |
| 04/15/15 | Annual review; position statements and references updated; formatting changes. |
| 09/15/15 | Revision; update position statement and references; formatting changes. |
| 11/15/15 | Revision; coding section updated. |

| | |
|---|---|
| 12/15/16 | Revision; title, description, position statements, and references updated; formatting changes. |
| 01/01/17 | Annual CPT/HCPCS update. Added 81422. |
| 07/01/18 | Quarterly CPT/HCPCS update. Added code 0060U. |
| 08/01/18 | Revision; ICD10 codes added. |
| 10/15/18 | Revision; coverage statement, description, coding, and references updated. |
| 01/01/20 | Annual CPT/HCPCS coding update. Deleted code 0009M. |
| 04/01/20 | Quarterly CPT/HCPCS update. Added code 0168U. |
| 11/15/20 | Review; Position statements and references updated. |
| 10/01/21 | Quarterly CPT/HCPCS update. Deleted code 0168U. |
| 11/15/21 | Review: Position statements maintained and references updated. |
| 02/15/23 | Review: Position statements, description, coding, and references updated. |
| 10/15/23 | Review: Coverage position statement, coding, and references updated. |
| 10/15/24 | Review: NIPT for single gene disorders position statement updated; description and references updated. |
| 07/15/25 | Review: Position statement for RhD genotyping added; position statements and title updated; description, coding, and references updated. |