BlueCross BlueShield Nebraska

GENETIC TESTING: PRENATAL CELL-FREE DNA TESTING (RECOMMEND PREAUTHORIZATION)

V.17

V.17 GENETIC TESTING: PRENATAL CELL-FREE DNA TESTING (RECOMMEND PREAUTHORIZATION)

Other common names for this test include: Non-invasive Prenatal Testing (NIPT), Cell-free Fetal DNA Testing (cffDNA)

Dates

Original Effective
12-26-2013
Last Review
08-07-2024
Next Review
08-11-2025

DESCRIPTION

Prenatal cell-free DNA testing (prenatal cfDNA) is a sequencing test performed on placental cell-free DNA found in maternal serum and is most commonly used to screen for fetal aneuploidy (trisomy 21, trisomy 13, and trisomy 18). Sex chromosomes are also screened for fetal sex determination and sex chromosome aneuploidy. Prenatal cfDNA is a screening test and does not provide definitive diagnosis for a fetus. When prenatal cfDNA is positive, or high risk, for a genetic abnormality, the fetus is at increased risk for that condition. Further testing via karyotype, fluorescent in situ hybridization (FISH), or chromosomal microarray (CMA) would be necessary to exclude the possibility of a false-positive.

Before testing, guidelines recommend that pregnant people be counseled about the risk of a false-positive result. False-positive findings have been associated with several factors, including placental

Prenatal cfDNA testing has expanded to include microdeletion and microduplication syndromes, as well as single-gene disorders, although this is an area of ongoing research. Prenatal cfDNA has also expanded to predict twin zygosity (i.e., monozygotic versus dizygotic twins). Monozygotic twins have a higher risk for certain complications, such as twin-twin transfusion syndrome (TTTS).

Prenatal screening can also be performed via maternal serum screening (MSS), which examines levels of various analytes produced by the fetus and placenta and provides risks for certain genetic conditions and birth defects.

REFERENCE TABLE

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

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes
Prenatal Cell-free DNA Testing for Chromosome 13, 18, 21, X and Y Aneuploidies	Vasistera (Natera)	0327U	O09, O28, O30 O35, Q90-Q99 Z34, Z36.0
	Panorama Prenatal Panel (with or without twin zygosity testing) (Natera)	81420, 0060U (twin zygosity only)	
	Harmony Prenatal Test (BioReference Laboratories)	81507	
Prenatal Cell-free DNA Testing for Microdeletions	Panorama Extended Panel (Natera)	81422	O09, O28, O35 Q90-Q99, Z34, Z36.0
	MaterniT21 Plus Core + ESS (LabCorp)		
	Prequel Prenatal Screen: Microdeletions (Myriad Genetics)		
Prenatal Cell-free DNA Testing for Single-gene Disorders	Vistara - Single-Gene NIPT (Natera)	81302, 81404, 81405, 81406, 81407, 81408, 81442	O09, O28, O30 O35, Q90-Q99 Z34, Z36.04
	PreSeek Non-invasive Prenatal Gene Sequencing Screen (Baylor Genetics, LLC)		
	UNITY Fetal Antigen NIPT	0488U	

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RELATED POLICIES

This policy document provides coverage criteria for Non-Invasive Prenatal Screening (NIPS). Please refer to:

- ***V.61 - Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for criteria related to circulating tumor DNA (ctDNA) or circulating tumor cell testing performed on peripheral blood for cancer diagnosis, management and surveillance.
- ***V.30 - Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***V.31 - Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to carrier screening for genetic disorders.
- ***V.75 - Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***V.62 - Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic genetic testing in the postnatal period.
- ***V.74 - Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to non-invasive prenatal screening that is not specifically discussed in this or other non-general policies, including known familial variant testing.

POLICY

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I. Prenatal cell-free DNA testing for 13, 18, 21, X and Y aneuploidy (81420, 81507, 0327U) may be considered **medically necessary** when:

A. The member has a singleton or twin pregnancy, **AND**

B. The member has NOT previously had cell-free DNA screening in the current pregnancy.

II. Prenatal cell-free DNA testing to predict twin zygosity (0060U) is considered **investigational.**

III. Prenatal cell-free DNA testing is considered **investigational** for all other indications, including the following:

A. For all other aneuploides (other than trisomy 13,18, 21)

B. For multiple gestation pregnancies (triplets or higher)

C. Prenatal cell-free DNA performed simultaneously with maternal serum screening

D. Use on a singleton pregnancy with a known vanishing twin

E. For the sole purpose of fetal sex determination

Prenatal Cell-free Testing for Microdeletions

I. Prenatal cell-free DNA testing for microdeletions and microduplications (81422) is considered **investigational.**

Prenatal Cell-free DNA Testing for Single-gene Disorders

I. Prenatal cell-free DNA testing for mutations associated with single gene disorders (81302, 81404, 81405, 81406, 81407, 81408, 81442) is considered **investigational.**

DEFINITIONS

Prenatal Cell-free DNA Testing is a screening test that is used to determine the risk of specific genetic disorders by analyzing traces of cell-free DNA (cfDNA) in a pregnant woman's blood.

Sequencing tests use 1 of 2 general approaches to analyze cell-free DNA. The most widely used technique to date uses massively parallel sequencing (MPS; also known as next-generation or "next gen" sequencing). The second general approach uses the single nucleotide polymorphism (SNP) method.

Singleton Pregnancy is a pregnancy with one fetus.

pregnancy complications, such as twin-twin transfusion syndrome (TTTS).

BACKGROUND

Prenatal Cell-free DNA Testing for Chromosome 13, 18, 21, X and Y Aneuploidies

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

ACOG and SMFM (2020) released a joint practice bulletin (No. 226) with the following recommendations for screening for fetal chromosomal abnormalities:

“The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):

> -Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cell-free DNA testing is not equivalent to diagnostic testing.” (p. e63)

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

> -“Cell-free DNA screening can be performed in twin pregnancies. Overall, performance of screening for trisomy 21 by cell-free DNA in twin pregnancies is encouraging, but the total number of reported affected cases is small. Given the small number of affected cases it is difficult to determine an accurate detection rate for trisomy 18 and 13. (p. e64)

Regarding prenatal screening for multiple gestation pregnancies of triplets or higher, Practice Bulletin No. 226 also states: “...there are no data available for serum screening for higher-order multiple gestations such as triplets and quadruplets.” (p. e59)

Regarding screening a pregnancy with a vanishing twin: “In a patient with both a vanishing twin and a viable intrauterine pregnancy, cell-free DNA screening is not advised because of the high risk for aneuploidy in the nonviable sac or embryo, which can lead to false-positive results.” (p. e53)

have multiple screening tests performed simultaneously." (p. e49)

American College of Medical Genetics and Genomics (ACMG)

ACMG (2016) published a position statement on noninvasive prenatal screening (NIPS) for fetal aneuploidy.

ACMG recommends:

> -Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., T13, T18, and T21). (p. 1059)
> -Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS. (p. 1059)
> -Providers should make efforts to deter patients from selecting sex chromosome aneuploidy screening for the sole purpose of biologic sex identification in the absence of a clinical indication for this information (p. 1060)

Current ACMG practice guidelines (2022) "strongly recommends NIPS over traditional screening for all pregnant patients with singleton and twin gestations for fetal trisomies 21, 18, and 13 and strongly recommends NIPS be offered to patients to screen for fetal sex chromosome aneuploidy." (p. 1 and p. 5)

National Society for Genetic Counselors (NSGC)

The National Society for Genetic Counselors adopted the following statement updated in 2021 supporting prenatal cell-free DNA (cfDNA) screening as an option for pregnant patients:

> The National Society of Genetic Counselors believes that all pregnant patients, regardless of aneuploidy risk, should have access to prenatal aneuploidy screening using cell-free DNA (cfDNA)*. Healthcare providers should present cfDNA screening for aneuploidy within the context of other available prenatal screening and diagnostic testing options. Included in this discussion should be the option of pursuing diagnostic testing as a first line approach or declining all screening/testing. Pretest counseling should also include a discussion of the individual patient's values, preferences, and needs, as well as the benefits and limitations of cfDNA screening. Many factors influence cfDNA screening performance; therefore, it may not be appropriate for every clinical scenario. Additionally, some laboratories offer screening for conditions beyond common aneuploidies, so it is

> Patients who receive increased risk or inconclusive/atypical results should receive post-test genetic counseling with a knowledgeable healthcare provider, such as a genetic counselor. In such cases, confirmatory diagnostic testing may be indicated, and patients should be counseled that no irreversible actions should be taken based on the cfDNA screening alone.

Wojas, et al

In a 2022 study of 59,471 twin pregnancies, the authors stated: “Further research should determine the impact of the addition of first trimester zygosity assignment for twin pregnancies upon the accuracy of chorionicity assignment, and the differences in healthcare costs for pregnancies assigned either MZ [monozygotic] or DZ [dizygotic] genetic origin. Finally, there is limited information on the impact of zygosity (corrected for chorionicity) upon pregnancy outcome. Our study lays a foundation for such research, to better determine the degree to which these two factors contribute independently to complicated and normal outcomes.” (p. 1239)

Prenatal Cell-free DNA Testing for Microdeletions

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

ACOG and SMFM (2020) released a joint practice bulletin (No. 226) with the following recommendations for screening for fetal chromosomal abnormalities:

> Screening for a limited number of microdeletions with cell-free DNA is available; however, this testing has not been validated clinically and is not recommended. Although microdeletions are relatively common when considered in aggregate, cell-free DNA panels only include a few specific clinically significant microdeletions and these are very rare. Therefore, the PPV for these disorders is much lower than for common trisomies. (p. e53)

American College of Medical Genetics (ACMG)

The ACMG 2022 practice guideline, 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), includes a conditional

NIPS for this purpose, after a discussion about the benefits and limitations of screening and in the context of shared-decision making." (p. 5)

Concert Note

Overall, studies attempting to validate the clinical utility of microdeletion analysis via NIPS have overall shown low positive predictive values and higher false positive rates, likely because of the low prevalence of the individual targeted microdeletion syndromes in the general population.

At the present time, testing for microdeletions, including 22q11.2, via cell-free DNA testing has insufficient evidence in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

Prenatal Cell-free DNA Testing for Single-gene Disorders

The American College of Obstetricians and Gynecologists (ACOG)

ACOG issued a practice advisory for the use of cell-free DNA to screen for single-gene disorders (February 2019, reaffirmed October 2022 and September 2023), which states the following:

> The continued innovation in cell-free technology combined with the desire for a maternal blood test to predict the risk for fetal genetic disorders during a pregnancy has broadened the application of cell-free DNA screening beyond aneuploidy to single-gene disorders. Examples of single-gene disorders include various skeletal dysplasias, sickle cell disease and cystic fibrosis. 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.

_Maternal Serum Screening (MSS)

The American College of Obstetricians and Gynecologists (ACOG)

Specifically, these guidelines state: "Prenatal genetic screening (serum screening with or without nuchal translucency [NT] ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling [CVS] or amniocentesis] options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality." (p. 862)

The use of multiple screening approaches performed independently (e.g., a first-trimester screening test followed by a quad screen as an unlinked test) is not recommended because it will result in an unacceptably high positive screening rate and could deliver contradictory results. (p. 865)

Quick Code Search

Use this feature to find out if a procedure and diagnosis code pair will be approved, denied or held for review. Simply put in the procedure code, then the diagnosis code, then click "Add Code Pair". If the codes are listed in this policy, we will help you by showing a dropdown to help you.

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Diagnosis

Please type a diagnosis code

Enter at least the first 3 characters of the code

Add

CODES

+ **CPT-PLA**

+ **CPT4**

REFERENCES

and zygosity assignment using single-nucleotide polymorphism-based cell-free DNA: Lessons learned from 55,344 twin pregnancies. Prenat Diagn. 2022 Sep;42(10):1235-1241. doi: 10.1002/pd.6218. Epub 2022 Sep 7. PMID: 35997139; PMCID: PMC9541063.

2023

Dungan JS, Klugman S, Darilek 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;25(2):100336. doi:10.1016/j.gim.2022.11.004

2016

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*. 2016;18(10):1056-1065. doi:10.1038/gim.2016.97

2019

“Cell-free DNA to Screen for Single-Gene Disorders”. Practice Advisory from The American College of Obstetricians and Gynecologists. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2019/02/cell-free-dna-to-screen-for-single-gene-disorders Published February 2019. Reaffirmed October 2022.

2021

“Prenatal Cell-Free DNA Screening.” Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/prenatal-cell-free-dna-screening-1. Released October 11, 2016. Revised April 2021.

2020

American College of Obstetricians and Gynecologists’ Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. *Obstet Gynecol*. 2020;136(4):e48-e69. doi:10.1097/AOG.0000000000004084

REVISIONS

09-26-2024
Added new codes for 10/01/2024: 0488U, 0489U, 0494U

11-02-2023
Updated policy for 01/01/2024

09-27-2023
Changed "may be considered medically necessary" to "may be considered scientifically validated"

Added: "investigational when the above criteria is not met and for all other indications"

07-01-2023
Updated references and minor changes in policy.

01-01-2023
Minor changes to policy. Updated background and references. Effective 1/1/2023

07-11-2022
Added new code effective 07/01/2022: 0327U

07-01-2022
Minor changes to policy and updated position statements. Removed deleted code 0168U.

01-01-2022
Minor updates to policy, updated background and references and removed 81420 & 81507 from Codes section as these do not hold for review.

09-02-2021
Added investigational criteria for all other aneuploides

06-08-2021
Updated formatting, criteria remains the same

04-29-2020
Updated policy and format. Added codes 81302, 81303. 81442, 81479, 81599.

0009M from policy.

07-02-2018
Added new code 0060U as investigational

11-23-2016
adding 0009M to policy

08-19-2016
Trisomy 13, 18 and 21 is now approved for average and low risk patient population. Testing of sex chromosomes and microdeletions remain investigative.

02-18-2016
Added that routine screening for sex chromosomes and microdeletions is Investigative.

03-09-2015
added Materni21T Plus to policy

01-07-2015
Added new code for 2015: 81420

12-24-2013
New policy effective 12/26/2013