Dean Health Plan Coverage Policy

Policy Name:	**Genetic Testing: Non-Invasive Prenatal Screening (NIPS) MP9573** Other common names for this test include: Non-invasive Prenatal Testing (NIPT), Cell-free Fetal DNA Testing (cffDNA)
Effective Date:	**January 01, 2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by Dean Health Plan. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Dean Health Plan Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this medical policy see Provider Communications for additional information.
https://deancare.com/Providers/Provider-communications
Dean Health Plan medical policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

OVERVIEW

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 mosaicism, vanishing twin, or a confounding factor within the pregnant person (such as a genetic condition or malignancy).
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.

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POLICY 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.

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
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	1, 2, 3, 5, 6
	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	3, 5
	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	4
	PreSeek Non-invasive Prenatal Gene Sequencing Screen (Baylor Genetics, LLC)			
	UNITY Fetal Antigen NIPT	0488U		
	UNITY Fetal Risk Screen	0489U		
Maternal Serum Screening (MSS)	First Trimester Maternal Screen, Serum (Mayo Clinic Laboratories)	81508	O09, O28, O30, O35, Q90-Q99, Z34, Z36.0	3
	Quad Screen (Quest Diagnostics)	81509, 81510, 81511, 81512		
	Serum Integrated Screen, Part 2 (Quest Diagnostics)			
	Penta Screen (Quest Diagnostics)	81512		

OTHER RELATED POLICIES

This policy document provides coverage criteria for Prenatal Cell-free DNA Testing. Please refer to:

- ***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.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing.
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage criteria related to carrier screening for genetic disorders.
- ***Genetic Testing: Preimplantation Genetic Testing*** for coverage criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic genetic testing in the postnatal period.
- ***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.

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COVERAGE CRITERIA

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

I. Prenatal cell-free DNA testing for 13, 18, 21, X and Y aneuploidy (0327U, 81420, 81507) 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 aneuploidies (other than trisomy 13, 18, and 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.

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Prenatal Cell-free DNA Testing for Microdeletions

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

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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.**

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Maternal Serum Screening (MSS)

I. Maternal serum screening for aneuploidy using no more than one of the following one time per pregnancy is considered **medically necessary**:

   A. First trimester screening (free or total beta-HCG and PAPP-A) (81508)

   B. Second trimester screening (hCG, msAFP, uE3, and DIA) (81509, 81510, 81511, 81512)

   C. Integrated, stepwise sequential, or contingent sequential screening (81508, 81509, 81510, 81511, 81512)

   D. Penta screen (hCG, msAFP, uE3, DIA, ITA) (81512).

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PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

DEFINITIONS

1. **Noninvasive prenatal screening (NIPS)** 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.
2. **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.
3. **Singleton pregnancy** is a pregnancy with one fetus.
4. **Twin zygosity** testing is used to predict the degree of genetic similarity within each pair (i.e., monozygotic versus dizygotic). Monozygotic (genetically identical twins) are at a higher risk for pregnancy complications, such as twin-twin transfusion syndrome (TTTS).

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BACKGROUND AND RATIONALE

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)

The Practice Bulletin No. 226 also notes that "[i]f screening is accepted, patients should have one prenatal screening approach, and should not 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 essential to consider the test's positive predictive value, particularly when the prevalence of the disorder is low.
>
> 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 recommendation, suggesting 22q11.2 deletion syndrome be offered to all patients. The guideline defines a conditional recommendation as follows: “most patients would request this testing and most clinicians would offer 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)

ACOG provided an updated position statement (number 226) regarding Screening for Fetal Chromosomal Abnormalities.

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)

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REFERENCES

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2. “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.
3. 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):859-867. doi:10.1097/AOG.0000000000004084.
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5. 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
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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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