# GENETIC TESTING: NON-INVASIVE PRENATAL SCREENING (NIPS)

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

## OVERVIEW

Non-invasive prenatal screening (NIPS) 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. NIPS is a screening test and does not provide definitive diagnosis for a fetus. When NIPS is positive, or high risk, for a genetic abnormality, the fetus is at increased risk for that condition. Further testing would be necessary to exclude the possibility of a false-positive.

NIPS has recently expanded to include microdeletion and microduplication syndromes, as well as single-gene disorders, although this is an area of ongoing research. NIPS 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).

## POLICY REFERENCE TABLE

Below are a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

| Coverage Criteria Sections | Example Tests (Labs) | Common CPT Codes | Common ICD Codes | Ref |
|---|---|---|---|---|
| Non-invasive Prenatal Screening (NIPS) for Trisomy 13, 18, and 21 | Panorama (Natera) | 81420, 0060U | O09, O28, O30, O35, Q90-Q99, Z34, Z36.0 | 1, 2, 3, 4, 5 |
| | MaterniT21 PLUS (Integrated Genetics) | 81420, 81479 | | |
| | Innatal Prenatal Screen (Progenity) | | | |

| | | | | |
|---|---|---|---|---|
| | Prequel Prenatal Screen (Myriad) | | | |
| | Invitae NIPS for Singleton Pregnancies (chromosomes 13, 18, 21) - Primary + Invitae NIPS for Singleton Pregnancies (chromosomes 13, 18, 21) (Invitae) | | | |
| | Harmony (Ariosa) | 81507 | | |
| Non-invasive Prenatal Screening (NIPS) for Microdeletions | Panorama - with microdeletion syndromes (Natera) | 81422, 0060U | O09, O28, O30, O35, Q90-Q99, Z34, Z36.0 | 6 |
| | QNatal Advanced (Quest) | 81422 | | |
| | MaterniT21 Plus Core + ESS (Integrated Genetics) | | | |
| | Prequel Prenatal Screen + Microdeletions (Myriad) | | | |
| | Invitae NIPS for Singleton Pregnancies (chromosomes 13, 18, 21) - Primary + for Select Microdeletions (1p36, 4p16.3, 5p15.2, 15q11.2, 22q11.2) (Invitae) | | | |
| Non-invasive Prenatal Screening (NIPS) for Single-Gene Disorders | Vistara (Point Mutation NIPT) (Natera) | 81302, 81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81442, 81479 | O09, O28, O30, O35, Q90-Q99, Z34, Z36.0 | 7 |
| | PreSeek Non-invasive Prenatal Gene Sequencing Screen (Baylor Miraca Genetics Laboratories) | | | |
| | Resura Prenatal Test (Progenity Inc) | 81403 | | |
| Maternal Serum Screening (MSS) | First Trimester Serum Screening Second Trimester Serum Screening Integrated Screening | 81508, 81509, 81510, 81511, 81512 | O09, O28, O30, O35, Q90-Q99, Z34, Z36.0 | 5 |

# OTHER RELATED POLICIES

This policy document provides coverage criteria for Non-Invasive Prenatal Screening (NIPS). 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 Testing*** for coverage criteria related to non-invasive prenatal screening that is not specifically discussed in this or other non-general policies.

# COVERAGE CRITERIA

## Non-invasive Prenatal Screening (NIPS) for Trisomy 13, 18, and 21

I. Noninvasive Prenatal Screening (NIPS) for trisomy 13, 18, and 21 (81420, 81507, 0168U) may be considered **medically necessary** when:

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

   B. The member has received appropriate counseling about the benefits and limitations of this test by a prenatal care provider, a trained designee, or a genetic counselor.

II. NIPS for multiple gestation pregnancies (triplets or higher) or to predict twin zygosity (see definitions) (0060U) is considered **investigational**.

III. NIPS is considered **investigational** for all other indications, including the following:

A. For all other aneuploidies (other than trisomy 13, 18, and 21)
B. For the sole purpose of fetal sex determination
C. NIPS performed simultaneously with maternal serum screening
D. NIPS performed after a diagnostic test has been performed (e.g., amniocentesis, CVS, or PUBS)
E. Use on a singleton pregnancy with a known vanishing twin

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## Non-invasive Prenatal Screening (NIPS) for Microdeletions

I. NIPS for microdeletion and microduplications (81422) is considered **investigational**.

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## Non-invasive Prenatal Screening (NIPS) for Single-gene Disorders

I. NIPS for mutations associated with single gene disorders (81302, 81400, 81401, 81402, 81403, 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)

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# NOTES AND DEFINITIONS

**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.

**Sequencing-based 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.

**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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# CLINICAL CONSIDERATIONS

More than one cell-free DNA screen performed per pregnancy (defined by no more than one paid test per pregnancy) is not medically indicated.

NIPS does not assess the risk of neural tube defects (NTDs). Guidelines recommend that patients should continue to be offered screening for NTDs via ultrasound or maternal serum alpha fetoprotein (msAFP).

NIPS is a screening test and indicates an increased or decreased risk for the condition(s) being screened. NIPS is not diagnostic for any condition and pregnancy management decisions should not be based solely on the results of cell-free DNA screening. Karyotyping, FISH, or CMA would be necessary to exclude the possibility of a false-positive. Before testing, guidelines recommend that women be counseled about the risk of a false-positive result. False-positive findings have been associated with

factors, including placental mosaicism, vanishing twin, maternal genetic condition, and maternal malignancy.

ACOG Practice Guideline 226 (2020) recommends that all patients receive information on the risks and benefits of various methods of prenatal screening and diagnostic testing for fetal aneuploidies, including the option of no testing. ACOG also recommends that patients with indeterminate or uninterpretable (ie, "no call") cell-free DNA test results be referred for genetic counseling and offered ultrasound evaluation and diagnostic testing because "no-call" findings have been associated with an increased risk of aneuploidy.

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# BACKGROUND AND RATIONALE

**Practice Guidelines and Position Statements**

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

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (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):

- 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. After review and discussion, every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing.
- If screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously.
- 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.

- All patients should be offered a second-trimester ultrasound for fetal structural defects, since these may occur with or without fetal aneuploidy; ideally this is performed between 18 and 22 weeks of gestation (with or without second-trimester maternal serum alphafetoprotein).
- Patients with a positive screening test result for fetal aneuploidy should undergo genetic counseling and a comprehensive ultrasound evaluation with an opportunity for diagnostic testing to confirm results.
- Patients with a negative screening test result should be made aware that this substantially decreases their risk of the targeted aneuploidy but does not ensure that the fetus is unaffected. The potential for a fetus to be affected by genetic disorders that are not evaluated by the screening or diagnostic test should also be reviewed. Even if patients have a negative screening test result, they may choose diagnostic testing later in pregnancy, particularly if additional findings become evident such as fetal anomalies identified on ultrasound examination.
- Patients whose cell-free DNA screening test results are not reported by the laboratory or are uninterpretable (a nocall test result) should be informed that test failure is associated with an increased risk of aneuploidy, receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing.
- If an enlarged nuchal translucency or an anomaly is identified on ultrasound examination, the patient should be offered genetic counseling and diagnostic testing for genetic conditions as well as a comprehensive ultrasound evaluation including detailed ultrasonography at 18–22 weeks of gestation to assess for structural abnormalities.

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

- The use of cell-free DNA screening as follow-up for patients with a screen positive serum analyte screening test result is an option for patients who want to avoid a diagnostic test. However, patients should be informed that this approach may delay definitive diagnosis and will fail to identify some fetuses with chromosomal abnormalities.
- In clinical situations of an isolated soft ultrasonographic marker (such as echogenic cardiac focus, choroid plexus cyst, pyelectasis, short humerus or femur length) where aneuploidy screening has not been performed, the patient should be counseled regarding the risk of aneuploidy associated with the finding and cell-free DNA, quad screen testing, or amniocentesis should be offered. If aneuploidy testing is performed and is low-risk, then no further risk assessment is

needed. If more than one marker is identified, then genetic counseling, maternal–fetal medicine consultation, or both are recommended.
- No method of aneuploidy screening that includes a serum sample is as accurate in twin gestations as it is in singleton pregnancies; this information should be incorporated into pretest counseling for patients with multiple gestations.
- 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.
- Because preimplantation genetic testing is not uniformly accurate, prenatal screening and prenatal diagnosis should be offered to all patients regardless of previous preimplantation genetic testing.

The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):

- The use of multiple serum screening approaches performed independently (eg, 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 risk estimates.
- In multifetal gestations, if a fetal demise, vanishing twin, or anomaly is identified in one fetus, there is a significant risk of an inaccurate test result if serum based aneuploidy screening or cell-free DNA is used. This information should be reviewed with the patient and diagnostic testing should be offered.
- Patients with unusual or multiple aneuploidies detected by cell-free DNA should be referred for genetic counseling and maternal–fetal medicine consultation.

American College of Medical Genetics and Genomics (ACMG)

The American College of Medical Genetics and Genomics (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).
- Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS.
- Offering diagnostic testing when a positive screening test result is reported after NIPS.

- Providing accurate, balanced, up-to-date information, at an appropriate literacy level, when a fetus is diagnosed with a chromosomal or genomic variation in an effort to educate prospective parents about the condition of concern. These materials should reflect the medical and psychosocial implications of the diagnosis.

ACMG recommended against using NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21.

The American College of Medical Genetics and Genomics (2009) published a practice guideline for screening for fetal aneuploidy and neural tube defects that recommended the following:

- First trimester screening (NT measurement, PAPP-A, and hCG) is an acceptable, effective approach for screening for fetal aneuploidy if a woman presents early in pregnancy (before 14 weeks' gestation).
- Women who decide to undergo first trimester screening and/or CVS should be offered MSAFP screening and/or an ultrasound for the detection of neural tube defects between 15 and 20 weeks' gestation.
- First trimester screening or second trimester screening can be used in multifetal pregnancies; however, women should be made aware of the limitations of screening in this setting.

In 2013, the American College of Medical Genetics and Genomics statement on noninvasive prenatal screening for fetal aneuploidy included the following regarding counseling for aneuploidies:

Pretest information should be provided by a prenatal care provider, a trained designee, or a genetic counselor to ensure patients make informed decisions. Aneuploidy screening is not a routine prenatal test; it is acceptable for patients to decline screening.

Pretest information should include:

- A brief explanation of the purpose of NIPS.
- Advantages of NIPS as compared with maternal serum analyte screening.
    - On the basis of available data, detection rates appear to be higher.

    - There is a high negative predictive value for Down syndrome. This may be important for patients seeking to avoid the risks (e.g., fetal loss) inherent with invasive testing.
    - NIPS has a lower false-positive rate, meaning fewer women will receive a "positive" screen, necessitating fewer invasive procedures.
    - Risk assessment is less dependent on gestational age.
- Considerations for follow-up invasive testing if NIPS indicates an increased risk for aneuploidy.
- Limitations of NIPS.

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.

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 March 2020), 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."

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# REFERENCES

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