GENETIC TESTING: NON-INVASIVE PRENATAL SCREENING (NIPS)

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

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
	Vasistera (Natera)	0327U		

Non-invasive Prenatal Screening (NIPS) for Chromosome 13, 18, 21, X and Y Aneuploidies	Panorama Prenatal Panel (Natera)	81420, 0060U	O09, O28, O30, O35, Q90-Q99, Z34, Z36.0	1, 2, 3, 6
	Singleton NIPS (chromosomes 13, 18, 21) (Invitae)			
	MaterniT21 PLUS (Integrated Genetics)			
	Harmony (BioReference Laboratories)	81507		
Non-invasive Prenatal Screening (NIPS) for Microdeletions	Panorama - with microdeletion syndromes (Natera)	81420, 81422, 0060U	O09, O28, O35, Q90-Q99, Z34, Z36.0	3
	MaterniT21 Plus Core + ESS (Integrated Genetics)			
	Prequel Prenatal Screen + Microdeletions (Myriad)			
Non-invasive Prenatal Screening (NIPS) for Single-Gene Disorders	Vistara (Single-Gene NIPT) (Natera)	81302, 81404, 81406, 81407, 81408, 81442	O09, O28, O30, O35, Q90-Q99, Z34, Z36.0	4
	PreSeek Non-invasive Prenatal Gene Sequencing Screen (Baylor Miraca Genetics Laboratories)			
Maternal Serum Screening (MSS)	First Trimester Screen, HCG (Quest Diagnostics)	81508	O09, O28, O30, O35, Q90-Q99, Z34, Z36.0	5
	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 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 Chromosome 13, 18, 21, X and Y Aneuploidies

I. Noninvasive Prenatal Screening (NIPS) for trisomy 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 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 to predict twin zygosity (0060U) is considered **investigational**.

III. NIPS for multiple gestation pregnancies (triplets or higher) is considered **investigational**.

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

A. For all other aneuploidies (other than trisomy 13, 18, and 21)
B. NIPS performed simultaneously with maternal serum screening
C. Use on a singleton pregnancy with a known vanishing twin
D. For the sole purpose of fetal sex determination

back to top

Non-invasive Prenatal Screening (NIPS) for Microdeletions

I. NIPS for microdeletion and microduplications (81422, 0060U) is considered **investigational**.

back to top

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

I. NIPS for mutations associated with single gene disorders (81302, 81404, 81406, 81407, 81408, 81442) is considered **investigational.**

back to top

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)

back to top

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.

Singleton pregnancy is a pregnancy with one fetus.

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).

back to top

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.

back to top

BACKGROUND AND RATIONALE

Non-invasive Prenatal Screening (NIPS) for Chromosome 13, 18, 21, X and Y Aneuploidy

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). (page 1059)
- Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS. (page 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.

Non-invasive Prenatal Screening (NIPS) 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)

Non-invasive Prenatal Screening (NIPS) 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 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.

Maternal Serum Screening

The American College of Obstetricians and Gynecologists

- All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age. The choice of screening test is affected by many factors, including a desire for information before delivery, prior obstetric history, family history, and the number of fetuses. Other factors to be considered include gestational age at presentation, the availability of a reliable nuchal translucency measurement, screening test sensitivity and limitations, the cost of screening, the constraints of long-term care of an affected child, and options for pregnancy care or termination for an abnormal diagnostic test result. No one test is superior for all test characteristics

and not every test is available at all centers. Each test has advantages and disadvantages that should be discussed with each patient, with the appropriate test offered based on her concerns, needs, and values. (ACOG 163, pg 6)

- Stepwise and Contingent screening was developed to maintain a high detection rate using the combined first- and second- trimester screening approach while also reporting the patient's first-trimester screening test risk, which allows for earlier management options. Using stepwise sequential screening, the patient is given a preliminary risk estimate after completion of the first-trimester analytes and nuchal translucency screening. If the first-trimester screening result indicates that the risk of aneuploidy is greater than the laboratory-derived positive screening cutoff, the patient is notified and offered a diagnostic test or cell-free DNA screening, and the screening protocol is discontinued. If the patient has a lower risk than the cut off level, they are informed that they have received a negative screening test result and proceeds to quad screening in the second trimester. Sequential screening has a detection rate of 91–93% with a positive screening test result rate of 4–5%. (ACOG 163, p. 5)
- In locations where a nuchal translucency measurement by a certified ultrasonographer is unavailable, or if fetal position, maternal body habitus, or imaging properties preclude an accurate nuchal translucency measurement, serum integrated screening can be offered. (ACOG 163, p 5)

back to top

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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.

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back to top