CONCERT 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

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Reference Number: LA.CP.CG.15
Date of Last Revision 06/24

Coding implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 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).

NIPS has 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

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of

any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

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

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Non-invasive Prenatal Screening (NIPS) 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, 7
	Panorama Prenatal Panel (with or without twin zygosity testing) (Natera)	81420, 0060U* (twin zygosity only)		
	Singleton NIPS (chromosomes 13, 18, 21) (Invitae)			
	MaterniT21 PLUS (Integrated Genetics)			
	Harmony Prenatal Test (BioReference Laboratories)	81507		
Non-invasive Prenatal Screening (NIPS) for Microdeletions	Panorama Extended Panel (Natera)	81422*	O09, O28, O35, Q90-Q99, Z34, Z36.0	3, 5, 6
	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*, 81405*, 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 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 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 criteria related to carrier screening for genetic disorders.
- ***Genetic Testing: Preimplantation Genetic Testing*** for criteria related to genetic testing of embryos prior to in vitro fertilization.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to diagnostic genetic testing in the postnatal period.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to non-invasive prenatal screening that is not specifically discussed in this or other non-general policies.

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CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

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

I. Noninvasive Prenatal Screening (NIPS) for 13, 18, 21, X and Y aneuploidy (81420, 81507, 0327U) may be considered **medically necessary** when:

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

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

II. NIPS to predict twin zygosity (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 multiple gestation pregnancies (triplets or higher)
C. NIPS 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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Non-invasive Prenatal Screening (NIPS) for Microdeletions

I. NIPS for microdeletions 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, 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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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

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.

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)

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)

American College of Medical Genetics (ACMG)

The ACMG practice guideline from 2023 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. 19)

Furthermore, the ACMG statement discusses a study (Dar, et al, 2022) that assessed the performance of SNP-based NGS and included more than 18,000 subjects. Results of the analysis demonstrated a 0.05% false positive rate and a 52.6% positive predictive value. (pages 5-6). Specifically, the study quoted a positive predictive value of 21% for DiGeorge syndrome. (Petersen, et al 2017, p. 691.e1 and e4) However, 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 non-invasive prenatal screening has **insufficient** evidence in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care. Further studies are needed to determine the sensitivity and specificity of the test.

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 October 2022), 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 (ACOG)

The American College of Obstetricians and Gynecologists (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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Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Converted corporate to local policy.	09/23	11/27/23	
Semi-annual review. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Overview: added "via karyotype, FISH, or CMA"; added "Before testing, guidelines recommend…"; removed "recently". For Policy Reference Table: under Non-invasive Prenatal Screening (NIPS) for Chromosome 13, 18, 21, X and Y Aneuploidies added "with or without twin zygosity testing"; added "twin zygosity only"; added "Prenatal Test"; under Non-invasive Prenatal Screening (NIPS) for Microdeletions replaced "with microdeletion syndromes" with "Extended Panel"; removed "81420"; added "twin zygosity only"; under Non-invasive Prenatal Screening (NIPS) for Single-Gene Disorders added "81405". For Other Related Policies: added "and Molecular". For Criteria; Non-invasive Prenatal Screening (NIPS) for Chromosome 13, 18, 21, X and Y Aneuploidies: under I. removed "trisomy"; under I.B. removed "received appropriate counseling…"; added "NOT previously had cell-free DNA…"; under III. Added "B. For multiple gestation pregnancies…". For Notes and Definitions: removed "Clinical Considerations…". For Background and Rationale: added "American College of Medical Genetics (ACMG)…"; under Non-invasive Prenatal Screening (NIPS) for Single Gene Disorders: replaced "March 2020" with "October 2022"; under Maternal Serum Screening: removed "All women should be offered…"; added "The American College of Obstetricians…".	11/23	2/27/24	
Semi-annual review. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	06/24	9/17/24	10/17/24

References

1. 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
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
4. "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.
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
6. Petersen AK, Cheung SW, Smith JL, et al. Positive predictive value estimates for cell-free noninvasive prenatal screening from data of a large referral genetic diagnostic laboratory. *Am J Obstet Gynecol*. 2017;217(6):691.e1-691.e6. doi:10.1016/j.ajog.2017.10.005
7. Wojas A, Martin KA, Koyen Malashevich A, Hashimoto K, Parmar S, White R, Demko Z, Billings P, Jelsema R, Rebarber A. Clinician-reported chorionicity 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.

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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