Non-Invasive Prenatal Screening

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Introduction

Non-invasive prenatal screening (NIPS) is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Non-Invasive Prenatal Screening for Fetal Aneuploidy	81420
Non-Invasive Prenatal Screening for Fetal Aneuploidy with Risk Score	81507
Non-Invasive Prenatal Screening for Fetal Chromosomal Microdeletions	81422
Non-Invasive Prenatal Screening for Single-Gene Mutations	81105-81479
UNITY Fetal Risk Screen	0489U
Vasistera	0327U

Criteria

Introduction

Requests for non-invasive prenatal screening (NIPS) are reviewed using the following criteria.

Cell-free DNA-based prenatal screening for fetal aneuploidy

- Genetic Counseling:

NIPT

  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Prenatal Screening:
  - Prenatal cell-free DNA screening for fetal aneuploidy (e.g. trisomy 13, 18, and 21) is medically necessary when all of the following criteria are met:
    - Singleton or twin pregnancy, AND
    - Gestational age within the window validated by the selected testing laboratory, AND
    - Rendering laboratory is a qualified provider of service per the Health Plan policy.
- Prenatal cell-free DNA screening is not medically necessary in the following circumstances:
  - A pregnancy in which a fetal demise has occurred
  - Triplet and higher-order multi-fetal gestation pregnancies
  - More than one prenatal cell-free DNA screen performed per pregnancy (exceptions for repeat screening will be considered on a case-by-case basis when requested due to initial results being unobtainable as a result of low fetal fraction)
  - When karyotyping, aneuploidy FISH, and/or cytogenomic microarray analysis (CMA) have already been performed on the pregnancy
- It is not medically necessary to perform maternal serum screening for aneuploidy and non-invasive prenatal screening (prenatal cell-free DNA screening) concurrently.
- Prenatal diagnosis by amniocentesis or CVS following NIPS is medically necessary when NIPS results are screen positive, inconclusive, or uninterpretable, or when additional information becomes available throughout the pregnancy that suggests additional risk factors.
- If non-invasive prenatal screening (prenatal cell-free DNA screening) has been successfully performed in the current pregnancy, other aneuploidy screening (by first or second trimester screening or integrated, step-wise sequential, or contingent sequential screening) is not medically necessary. Maternal serum screening for neural tube defects (AFP-only) is medically necessary.

Prenatal cell-free DNA screening for chromosome microdeletions

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.

- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Prenatal cell-free DNA screening for single-gene mutations

For information regarding fetal Rh(D) genotyping using NIPS, please see the guideline *Human Platelet and Red Blood Cell Antigen Genotyping*, as that testing is not addressed here.

For all other indications, this test is Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

Other Considerations

For information regarding prenatal maternal serum screening for aneuploidy and open neural tube defects, please refer to the guideline, *Prenatal Maternal Serum Screening*, as that testing is not addressed here.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Prenatal cell-free DNA screening is not reimbursable for pregnancies in which a fetal demise has occurred, or for triplet and other higher-order multiple gestations. These

are defined by the presence of one of the diagnosis codes from Table: *ICD Codes Indicating Fetal Demise and Triplet or Higher-Order Multiple Gestations*.

- Screening for aneuploidy of the X and Y chromosomes and/or detection of less common trisomies, are not separately reimbursable under these coverage guidelines. Additional procedure codes billed with cell-free DNA screening for this purpose are not eligible for reimbursement.
- Prenatal cell-free DNA screening for chromosome microdeletions (CPT: 81422) is not reimbursable.
- When prenatal cell-free DNA screening is otherwise reimbursable, the following limitations apply:
  - No more than one prenatal cell-free DNA screening is reimbursable per pregnancy, defined as no more than one paid prenatal cell-free DNA screen procedure code (e.g., 81420 or 81507) within 10 weeks.
  - Non-specific procedure codes (e.g. 81479, 81599) or any procedure codes that do not accurately describe the test methodology performed (e.g. 88271) are not eligible for reimbursement.

ICD Codes

ICD codes used for automated claims processing for this guideline.

Table: ICD Codes Indicating Fetal Demise and Triplet or Higher-Order Multiple Gestations

Codes and descriptions

Code or Range	Description
O30.1X	Triplet pregnancy
O30.2X	Quadruplet pregnancy
O31.00X0-O31.00X9	Papyraceous fetus, unspecified trimester
O31.01X0-O31.01X9	Papyraceous fetus, first trimester
O31.02X0-O31.02X9	Papyraceous fetus, second trimester
O31.03X0-O31.03X9	Papyraceous fetus, third trimester
O31.10X0-O31.10X9	Continuing pregnancy after spontaneous abortion of one fetus or more, unspecified trimester
O31.11X0-O31.11X9	Continuing pregnancy after spontaneous abortion of one fetus or more, first trimester

Code or Range	Description
O31.12X0-O31.12X9	Continuing pregnancy after spontaneous abortion of one fetus or more, second trimester
O31.13X0-O31.13X9	Continuing pregnancy after spontaneous abortion of one fetus or more, third trimester
O31.20X0-O31.20X9	Continuing pregnancy after intrauterine death of one fetus or more, unspecified trimester
O31.21X0-O31.21X9	Continuing pregnancy after intrauterine death of one fetus or more, first trimester
O31.22X0-O31.22X9	Continuing pregnancy after intrauterine death of one fetus or more, second trimester
O31.23X0-O31.23X9	Continuing pregnancy after intrauterine death of one fetus or more, third trimester
O31.30X0-O31.30X9	Continuing pregnancy after elective fetal reduction of one fetus or more, unspecified trimester
O31.31X0-O31.31X9	Continuing pregnancy after elective fetal reduction of one fetus or more, first trimester
O31.32X0-O31.32X9	Continuing pregnancy after elective fetal reduction of one fetus or more, second trimester
O31.33X0-O31.33X9	Continuing pregnancy after elective fetal reduction of one fetus or more, third trimester
O31.8X13	Other complications specific to multiple gestation, first trimester, fetus 3
O31.8X14	Other complications specific to multiple gestation, first trimester, fetus 4
O31.8X15	Other complications specific to multiple gestation, first trimester, fetus 5

Code or Range	Description
O31.8X23	Other complications specific to multiple gestation, second trimester, fetus 3
O31.8X24	Other complications specific to multiple gestation, second trimester, fetus 4
O31.8X25	Other complications specific to multiple gestation, second trimester, fetus 5
O31.8X33	Other complications specific to multiple gestation, third trimester, fetus 3
O31.8X34	Other complications specific to multiple gestation, third trimester, fetus 4
O31.8X35	Other complications specific to multiple gestation, third trimester, fetus 5
O31.8X93	Other complications specific to multiple gestation, unspecified trimester, fetus 3
O31.8X94	Other complications specific to multiple gestation, unspecified trimester, fetus 4
O31.8X95	Other complications specific to multiple gestation, unspecified trimester, fetus 5

What is a chromosome abnormality?

A chromosome abnormality is any difference in the structure, arrangement, or amount of genetic material packaged into the chromosomes.[1]

Humans typically have 23 pairs of chromosomes. Each chromosome has a characteristic appearance that should be the same in each person. Chromosome abnormalities can lead to a variety of developmental and reproductive disorders. Common chromosome abnormalities include Down syndrome (trisomy 21), trisomy 18, trisomy 13, Turner syndrome, and Klinefelter syndrome. Chromosome abnormalities occur in approximately 1 in 150 live births. A higher percentage of pregnancies are affected but lost during pregnancy.

About 6%-11% of stillbirths or neonatal deaths are associated with a chromosome abnormality.[2,3]

The risk of having a child with an extra chromosome, notably Down syndrome, increases as a woman gets older.[3] However, many babies with Down syndrome are

born to women under 35 and the risk of having a child with other types of chromosome abnormalities, such as Turner syndrome or 22q11 deletion syndrome, is not related to maternal age. Therefore, prenatal screening for Down syndrome and certain other chromosome abnormalities is now routinely offered to all pregnant women. As a result, prenatal diagnosis via amniocentesis or chorionic villus sampling (CVS) is now also an option for most pregnant women.

Test information

Introduction

Non-invasive prenatal screening (NIPS, also called prenatal cell-free DNA screening or cfDNA screening) is performed on a maternal plasma sample generally collected after 9 weeks' gestation.[4]

Methodology and Performance

Testing methodology relies on the presence of cell-free placental DNA in maternal circulation.[4] Approximately 10% of cell-free DNA in maternal circulation is of placental origin.[5]

Analysis of cell-free placental DNA is performed to identify pregnancies at increased risk for chromosomal aneuploidy. Detection rates for trisomies 21, 18, and 13 are greater than 98%, with false positive rates of less than 0.5%.[4]

Some laboratories also test for sex chromosome aneuploidies (such as Turner syndrome or Klinefelter syndrome) and rare chromosome microdeletion syndromes (such as 22q11 deletion syndrome or 1p36 microdeletion syndrome), with variable performance.

Each commercial or academic laboratory offering NIPS has a proprietary platform and bioinformatics pipeline.

Chromosome analysis via CVS and amniocentesis is also routinely available for diagnosis of fetal chromosome abnormalities in pregnancy.

Guidelines and evidence

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2023) published a practice guideline regarding Non Invasive Prenatal Screening (NIPS) and recommended the following:[5]

- "ACMG recommends NIPS over traditional screening methods for all pregnant patients with singleton gestation for fetal trisomies 21, 18, and 13 (Strong recommendation based on high certainty of evidence)"
- "ACMG recommends NIPS over traditional methods for trisomy screening in twin gestations (Strong recommendation, based on high certainty of evidence)"
- Regarding sex chromosome aneuploidies (SCAs): "ACMG recommends that NIPS be offered to patients with a singleton gestation to screen for fetal SCA (Strong recommendation, based on high certainty of evidence)"
- "ACMG suggests that NIPS for 22q11.2 deletion syndrome be offered to all patients (Conditional recommendation, based on moderate certainty of evidence)"
- Regarding other copy number variants (CNVs): "At this time, there is insufficient evidence to recommend routine screening for CNVs other than 22q11.2 deletions (No recommendation, owing to lack of clinically relevant evidence and validation)"
- Regarding rare autosomal trisomies (RATs): "At this time, there is insufficient evidence to recommend or not recommend NIPS for the identification of RATs (No recommendation, owing to lack of clinically relevant evidence)"
- Regarding pregnancies with a vanishing twin: "There was no evidence ... to support altering the option of NIPS in a pregnancy with a known vanishing twin, although the patient should be counseled that accuracy may be impacted. The American College of Obstetricians and Gynecologists states that NIPS should not be performed in such circumstances."

The American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG, 2019; reaffirmed September 2023) issued a practice advisory on the use of cell-free DNA to screen for single-gene disorders and stated the following:[6]

- "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."

The American College of Obstetricians and Gynecologists and Society for Maternal Fetal Medicine

In 2020, The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) published a joint practice bulletin and stated:[7]

- "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 chromosome abnormality." [Level A Recommendation: based on good and consistent scientific evidence]
- "If screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously." [Level A Recommendation: based on good and consistent scientific evidence]
- "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." [Level A Recommendation: based on good and consistent scientific evidence]
- "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." [Level B Recommendation: based on limited or inconsistent scientific evidence]
- "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." [Level C Recommendation: based primarily on consensus and expert opinion]

American Society of Human Genetics and European Society of Human Genetics

A 2015 joint statement by the American Society of Human Genetics (ASHG) and European Society of Human Genetics (ESHG) included the following recommendations:[8]

- "NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFTS. However, a positive NIPT result should not be regarded as a final diagnosis… Thus women should be advised to have a positive result confirmed through diagnostic testing, preferably by amniocentesis, if they are considering a possible termination of pregnancy."

- "Expanding NIPT-based prenatal screening to also report on sex chromosomal abnormalities and microdeletions not only raises ethical concerns related to information and counseling challenges but also risks reversing the important reduction in invasive testing achieved with implementation of NIPT for aneuploidy, and is therefore currently not recommended."

The International Society for Prenatal Diagnosis

The International Society for Prenatal Diagnosis (ISPD, 2023) issued a position statement on the use of NIPT for the detection of chromosomal conditions in singleton pregnancies that stated:[9]

- "NIPT is the most accurate screening test for the common autosomal aneuploidies (trisomies 21, 13 and 18) in unselected singleton populations, and those at known increased probability."
- "NIPT for the common autosomal aneuploidies performs sufficiently well to be offered in primary or contingent screening models."
- "FPR [false positive results] occur with NIPT. Therefore, ISPD strongly recommends that all patients with a high chance NIPT result have genetic counseling and diagnostic testing if they are considering termination of pregnancy."
- "NIPT for SCA [sex chromosome aneuploidy] is sufficiently accurate to be offered alongside autosomal aneuploidy screening with specific pretest counseling and consent."
- There is insufficient data to assess the performance and clinical utility of routine NIPT for rare autosomal trisomies, sub-chromosomal imbalances and microdeletion/duplication syndromes.

The ISPD issued a position statement (2020) on cfDNA screening for Down syndrome in twin and triplet pregnancies. The statement compared cfDNA screening to other screening methods available for multiple gestation pregnancies, focusing on test characteristics. This approach is in contrast to other professional guidelines that compare the performance of cfDNA in twin pregnancies to that reported for cfDNA screening in singleton pregnancies. ISPD summarized recommendations for evidence-based practices:[10]

- "The use of first trimester cfDNA screening for the common autosomal trisomies is appropriate for twin pregnancies due to sufficient evidence showing high detection and low false positive rates with high predictive values. Moderate."
- "The finding of an increased risk on a cfDNA screening test in multiple pregnancies should be followed by counseling and an offer of diagnostic testing to confirm results. Strong."

The National Society of Genetic Counselors

The National Society of Genetic Counselors (NSGC, 2021) issued a position statement regarding the use of prenatal cell-free DNA screening:[11]

- "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)."
- "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."

Society of Obstetricians and Gynaecologists of Canada

The Society of Obstetricians and Gynaecologists of Canada (SOGC, 2017) stated: "Routine cfDNA screening for fetal microdeletions is not currently recommended (II-2B)."[12,13]

Selected Relevant Publications

Selected relevant publications pertaining to twin pregnancies, microdeletion testing, and single gene testing.

Multiple Gestation Pregnancies

The evidence base for NIPS in twin pregnancies suggested that NIPS may be useful as a screening test for common aneuploidies. However, well-designed clinical validity and clinical utility studies evaluating the performance of NIPS in triplet and higher order multifetal pregnancies in the general obstetric population are needed. A systematic evidence-based review published by the American College of Medical Genetics and Genomics (ACMG, 2022) included 7 studies in a meta-analysis evaluating the performance of cfDNA screening for aneuploidy in multi-fetal gestations.[14] The authors stated: "The results from our meta-analyses show NIPS performance in this population [twin gestations] are generally comparable to performance in singleton pregnancies for T21, T18, and T13. Results for other aneuploidies or microdeletions were less frequently reported and no firm conclusions can be drawn about the performance of NIPS for these outcomes. Very limited data is available on triplets or higher order multiple gestations."

Microdeletion Syndromes

The evidence base for the use of NIPS for microdeletion detection was of low quality.[14-37] Several systematic reviews have concluded that the evidence is insufficient to draw firm conclusions related to the use of NIPS for microdeletion testing. Diagnostic performance estimates were highly variable, there was insufficient

utilization of reference testing in the available studies, and significant heterogeneity existed between studies due to differing NIPS methodologies, the number and type of deletions screened, and patient populations. Well-designed clinical validity studies with comprehensive reference test use in low-risk patient populations are needed along with clinical utility studies that evaluate pregnancy and postnatal outcomes. These studies should also allow for comparison of methodologies and the number and type of microdeletion/microduplication syndromes.

Single Gene Disorders

The strength of the available evidence for NIPS use in detecting single-gene disorders was low.[30,38--61] There are few clinical studies evaluating the performance of NIPS in detecting these disorders. The majority of available clinical studies have focused on targeted testing for common or familial variants; however, the number of studies screening for multiple monogenic disorders with NIPS is increasing. Sample failures and interpretation issues are common and related to a number of factors, including: low fetal fraction, difficulty distinguishing fetal from maternal variants, insufficient SNP numbers in the target region, and DNA recombination events. The evidence base is insufficient to permit definitive conclusions regarding the performance of NIPS to identify single-gene disorders. Large well-designed clinical validity and clinical utility studies evaluating NIPS for this indication in general obstetric and/or high-risk populations are needed.

Sex Chromosome Aneuploidies

The evidence base for NIPS use in SCA detection was of low quality.[34,62-64] Clinical performance data suggests that NIPS has high sensitivity and specificity for SCAs, but reported positive predictive values (PPVs) vary significantly based on subtype, test platform, and patient population. Accurate screening for Turner syndrome is difficult due to confined placental mosaicism and maternal somatic mosaicism, often leading to a low PPV and increased false positive results. Clinical utility data is limited and does not allow for assessment of the overall impact of SCA screening. Ethical concerns related to use of this screening include the challenges involved in provision of pre- and post-test parental counseling, the mild and highly variable phenotypic presentations of SCAs, increased rates of unnecessary invasive diagnostic testing, and a lack of consensus on therapeutic benefits for prenatally diagnosed patients.[65]

Vanishing Twin Pregnancies

The performance of non-invasive prenatal screening in vanishing twin pregnancies is relatively unknown. A systematic review of available literature notes pooled data for 1592 cases showed no report of discordant negative result. It also notes successful detection of common autosomal trisomies but with a higher false positive rate (attributed to the detection of cfDNA from the demised twin that was aneuploid).[66]

Note:

NIPT

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for non-invasive prenatal screening will ensure that testing will be available to those members most likely to benefit from the information provided by the assay. For those not meeting criteria, it ensures alternate management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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