MEDICAL POLICY

Medical Policy Title	**Non-Invasive Prenatal Testing**
Policy Number	**2.02.25**
Current Effective Date	**August 17, 2026**
Next Review Date	**April 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service.
(Link to Product Disclaimer)

This policy does not address non-targeted preconception or prenatal carrier screening panels for autosomal recessive and x-lined genetic disorders (e.g., CPT code 0449U). Please refer to CMP#4.01.03 Prenatal Genetic Testing.

POLICY STATEMENT(S)

I. Non-invasive prenatal testing (NIPT) utilizing the plasma of a pregnant member (i.e., cell free DNA) to screen for trisomy 21 (T21), trisomy 13 (T13), and trisomy (T18) is **medically appropriate** for those members with singleton pregnancies.

II. Serum analyte analysis combined with ultrasound for nuchal translucency (NT) measurement is **medically appropriate** for screening for T21, T13, and T18 in the first trimester of pregnancy.

III. Measurement of cell-free DNA for fetal genotyping for RhD antigen may be **medically appropriate** when **ALL** the following criteria are met:

- A. Pregnancy may be at risk for alloimmunization due to maternal RhD negative status or the presence of maternal red cell antigen antibodies;
- B. Paternal antigen typing is unavailable or heterozygous;
- C. Amniocentesis is declined or contraindicated.

IV. Screening for detection of chromosomal abnormalities using measurement of nuchal translucency is **not medically necessary**.

V. NIPT for the determination of twin zygosity is **not medically necessary** (CPT: 0060U).

VI. NIPT is **investigational** in **ALL** of the following scenarios:

- A. Multiple gestation pregnancies;
- B. Aneuploidies other than T21, T13, and T18;
- C. Microdeletions (e.g., DiGeorge syndrome, Cri-du-chat syndrome, Shprintzen syndrome, Prader-Willi/Angelman syndromes, Wolf-Hirschorn syndrome, 1p36 deletion syndrome) (CPT: 81422);
- D. Fetal sex chromosome aneuploidy (SCA);
- E. Single-gene disorder screening (e.g., Unity fetal risk screen [Billion To One])

F. Rolling circle replication cell-free fetal DNA screening (e.g., Vanadis NIPT);

G. Measurement of fetal nasal bone length.

RELATED POLICIES

Corporate Medical Policy

2.02.03 Genetic Testing for Inherited Disorders

4.01.03 Prenatal Genetic Testing

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

Noninvasive prenatal testing (NIPT) should only be offered in the context of informed consent, education, and counseling by a qualified provider, such as a certified genetic counselor. Abnormal NIPT results should be confirmed with chorionic villi sampling (CVS) or amniocentesis to exclude the possibility of a false positive NIPT result.

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Supporting documentation required:

The following factors will be considered when determining the medical appropriateness of a genetic test:

A. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.

B. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.

C. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).

D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.

E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any panel testing. If targeted testing has not been performed, rationale as to why panel testing is medically necessary should be documented.

DESCRIPTION

Aneuploidy is a chromosomal abnormality defined as the gain or loss of one or more chromosomes from the normal chromosome number within a fetus. Structural anomalies, failure to thrive, intellectual disability, and a shortened lifespan are among the list of potential outcomes for a newborn born with aneuploidy.

The most common aneuploidies involve three copies of one chromosome and are known as trisomy syndromes. The most common syndrome among live births is Trisomy 21 (Down syndrome) and occurs in one 1/700 live births (Centers for Disease and Prevention). The risk for Trisomy 18 (Patau syndrome) and Trisomy 13 (Edward's syndrome) are also detectable through screening but have a much lower live birth rate.

There is a wide array of screening available throughout pregnancy. Each screening option has differing advantages, as well as limitations. The prevalence of aneuploidy is greater earlier in the pregnancy, as it accounts for a large portion of early pregnancy loss and the risk increases as a pregnant patient ages. Early detection provides an opportunity for discussions regarding early intervention, pregnancy termination, or fetal loss; however, pregnant individuals must be provided comprehensive counseling that allows for informed decision-making, is centered around the individual's values, and goals, and includes the right to decline screening after counseling.

Biochemical Serum and Ultrasound Markers

The standard or primary screening for chromosomal abnormalities utilizes conventional serum tests of free beta-human chorionic gonadotropin (hCG), pregnancy-associated plasma protein-A(PAPP-A), and ultrasound imaging of fetal nuchal translucency (NT), the fluid-filled space measured around the dorsal aspect of the fetal neck. An enlarged nuchal translucency (greater than 3.0 mm/99th percentile of the crown to rump length) is independently associated with aneuploidy and structural malformations. The combined testing also considers the patient's age, positive family history of aneuploidy, and if a parent has a risk for translocation.

Screening via ultrasound for nasal bone identification or measurement has been used as an ancillary method to assess the risk of aneuploidy in the first trimester. The absence of fetal nasal bone is considered to be a positive test result, indicating an increased risk of aneuploidy. The inability to visualize the nasal bone is regarded as an unsuccessful examination, rather than a positive test result. Fetal nasal bone examination can be performed from 11 weeks to just before 14 weeks' gestation. It is sometimes recommended that, if the nasal bone is absent on ultrasound performed between 11- and 12-weeks' gestation, a second examination be done two weeks later.

Screening via Cell-Free DNA

An alternative to the standard screening is the use of sequencing-based tests- massively parallel sequencing (also known as next-generation sequencing (NGS)) (MPS), direct DNA analysis, and nucleotide variant-based methods to analyze fragments circulating in the pregnant patient's plasma. MPS uses an amplified polymerase chain reaction to map the fragments to the human genome to get the number of fragment counts per chromosome.

Rolling Circle Replication Cell-Free DNA Screening

Another proposed approach for screening of cell-free DNA (cfDNA) is with Vanadis NIPT (Vanadis Diagnostics, PerkinElmer, Sollentuna, Sweden). Vanadis NIPT does not require polymerase chain reaction (PCR) or sequencing but rather uses rolling-circle replication and digital technology. It consists of three instruments that automate the extraction, processing, imaging, and counting of fluorescent DNA molecules. It uses algorithms and software to calculate trisomy risk. This test is reported to eliminate PCR bias, elaborate sample preparation, and complex analysis; thereby, reducing costs and the need for additional resources.

Microdeletions

cfDNA is being evaluated for use in the detection of chromosome microdeletions. Microdeletions are copy number variants that result in differences in the number of copies of one or more sections of DNA, that result in DNA losses. Microdeletions are too small to be detected via microscopy or cytogenetic methods. There are many disorders, with varying clinical features which differ based on the chromosome and gene that are compromised. Disorders that are associated with microdeletion include, but are not limited to DiGeorge Syndrome, Cri-du-chat syndrome, Shprintzen syndrome, Prader-Willi/Angelman syndromes, Wolf-Hirschorn syndrome, and 1p36 deletion syndrome.

Fetal Sex Chromosome Aneuploidy (SCA)

SCA occurs when there is an abnormal number of sex chromosomes (X&Y). These X&Y chromosome variations are not typically inherited, and the exact cause of them is unknown. Similar to microdeletions, clinical features vary based on the specific sex chromosome variation, and the number of extra X or Y chromosomes, and can include physical malformations, cognitive and growth disorders, as well as sexual and infertility problems. Examples of fetal sex chromosome aneuploidy include but are not limited to Klinefelter syndrome (1/1000 births), Turner syndrome, Jakob syndrome, and Triple X syndrome.

Single Gene Disorders

Single-gene, or monogenic disorders, are caused by variations in a single gene and are rare but collectively are present in approximately 1% of births. Examples of single-gene disorders are Noonan syndrome and other Noonan spectrum disorders, skeletal disorders (e.g., Osteogenesis Imperfecta, achondroplasia), craniosynostosis syndromes, Cornelia de Lange syndrome, Alagille syndrome, tuberous sclerosis, epileptic encephalopathy, SYNGAP1-related intellectual disability, CHARGE syndrome, Sotos syndrome, and Rett syndrome. Using proprietary Quantitative Counting Template technology, the Unity Screen (Billion to One) tests for T21, T18, T13, sex chromosome aneuploidy, fetal sex, and fetal RhD status and can be reflexed to maternal carrier screening for recessively

inherited conditions: cystic fibrosis, spinal muscular atrophy, sickle cell disease, alpha thalassemia, beta thalassemia, and fragile x syndrome (optional) without the need for paternal testing. The test requires only a maternal blood sample and background information on prior risk factors to establish a proprietary personalized fetal risk score ranging from >9 in 10 risk to <1 in 20000 for the recessive conditions. The clinical presentation and severity of these disorders can vary widely. Some, but not all, can be detected via prenatal ultrasound.

Twin Zygosity

Twin gestations occur in approximately one in 30 live births in the United States and have a much greater risk of perinatal complications. Dizygotic (fraternal) twins occur from the ovulation and fertilization of two oocytes, which results in dichorionic placentation and two separate placentas while monochorionic (identical) twin pregnancies share their blood supply. Monochorionic twins account for about 20% of twin gestations and are at higher risk of structural defects, miscarriage, preterm delivery, and selective fetal growth restriction compared to dichorionic twins. Up to 15% of monochorionic twin pregnancies are affected by twin-to-twin transfusion syndrome (TTTS), a condition characterized by hypovolemia of one twin and hypervolemia of the other, given the uneven passing of blood between the twins. TTTS is estimated to occur in up to 15% of monochorionic twin pregnancies. In these twin pregnancies, fetal ultrasound examinations are necessary to monitor the development of TTTS as well as selective intrauterine growth restriction because these disorders have high morbidity and mortality and treatments are available that can improve outcomes. NIPT using cfDNA to determine zygosity in twin pregnancies could potentially inform decisions about early surveillance for TTTS and other monochorionic twin-related abnormalities, or could potentially assist in the assessment of chorionicity, which is the main determinant of perinatal outcome in twin pregnancies, when ultrasound findings are not certain.

Fetal RhD

Rhesus D (RhD)-negative women who are exposed to RhD-positive red blood cells can develop anti-RhD antibodies, which can cross the placenta and cause fetal anemia. If undiagnosed and untreated, alloimmunization can cause significant perinatal morbidity and mortality. Determining the RhD status of the fetus may guide subsequent management of the pregnancy. Rho(D) immune globulin (RhIG) is a medication used to prevent RhD isoimmunization in mothers who are RhD negative. RhIG is commonly referred to as 'anti-D'.

SUPPORTIVE LITERATURE

Biochemical Serum and Ultrasound Markers

Pregnant patients are routinely offered blood-based screening or invasive diagnostic testing for the identification of T21, T13 and T18. Historically, standard screening involves combinations of the pregnant patient's serum markers and fetal ultrasound done at various stages of pregnancy. The detection rate for various combinations of NIPT ranges from 60% to 96% with a 5% false-positive rate, which is higher than desirable. When tests indicate a high risk of trisomy, karyotyping of fetal tissue obtained by amniocentesis or chorionic villus sampling is required to confirm that a trisomy is present.

Two large, multi-center studies, the Serum, Urine, and Ultrasound Screening (SURUSS) study (Wald, et al 2003) and the Biochemistry, Ultrasound, and Nuchal Translucency (BUN) study (Wapner, RJ 2005), show similar or greater estimates of sensitivity of first-trimester screening when compared either directly to second-trimester screening or to historical estimates of second-trimester screening. The SURUSS study demonstrated that NT assessment alone is inferior to either second-trimester or first-trimester combined screening.

Results of the First and Second Trimester Evaluation of Risk (FASTER) trial (Malone, et al 2003), sponsored by the National Institute of Child Health and Human Development indicate that first-trimester combined screening at 11 weeks gestation is better than second-trimester quadruple screening. FASTER was a multicenter (15 U.S. hospitals), prospective study comparing the rates of detection of first and second-trimester noninvasive screening methods for Down syndrome for singleton pregnancies. Participants underwent first-trimester screening consisting of NT thickness together with maternal age, and serum levels of PAPP-A and β-hCG at 11-, 12-, and 13-weeks' gestation, and then underwent screening again at 15-to-18 weeks gestation. Patients were not informed of the results of the first-trimester screening until after the second-trimester screening was completed. Of 38,167 patients, a total of 117 fetuses were identified as having Down syndrome. Researchers compared the results of (1) first-trimester combined screening; (2) second-semester screening; (3) stepwise sequential screening with results provided after each test; (4) fully integrated screening with a single result provided; and (5) serum-integrated screen identical to fully integrated screening but without nuchal translucency. Rates of detection using first-trimester combined screening were: 87% at 11 weeks, 85% at 12 weeks, and 82% at 13 weeks. The rate of detection using second-trimester screening was 81%. The rate of detection using first-trimester stepwise sequential screening was 95%, using serum integrated screening was 88%, and using fully integrated screening was 96%. Both stepwise sequential screening and fully integrated screening techniques had high rates of detection with low false positive rates.

Fetal Nose Bone Assessment

Studies have found a high rate of successful imaging of the fetal nasal bone and an association between absent nasal bone and the presence of T21 in high-risk populations. However, there is insufficient evidence on the performance of fetal nasal bone assessment in average-risk populations. Of particular concern is the low performance of fetal nasal bone assessment in a subsample of the FASTER study conducted in the general population sample (Malone, et al 2004). Two studies conducted outside of the U.S. have found that when added to a first-trimester screening program evaluating pregnant patient's serum markers and NT, fetal nasal bone assessment can result in a modest decrease in the false-positive rate. Fetal nasal bone assessment has been proposed as a second stage of screening, to screen patients found to be at borderline risk using maternal serum markers and NT. Additional studies using this contingent approach are needed before conclusions can be drawn about its utility. In summary, given the uncertainty of test performance in average-risk populations and the lack of standardization in the approach to incorporating this test into a first-trimester screening program, the detection of fetal nasal bone is considered investigational.

There is a lack of current literature to evaluate the clinical utility of this assessment.

Screening via Cell-Free DNA

cfDNA is the most sensitive and specific screening test for T21, T13, and T18 and can be performed any time after nine to ten weeks of gestation. The detection rate is the same regardless of the population tested. Norton and colleagues (2015) studied a series of 15,841 patients with cfDNA results for T21 and compared it with a general population using first-trimester screening with NT and serum analytes. It was identified that cfDNA had a lower false positive rate (0.06% for cfDNA vs. 5.4% for serum screening) and a higher positive predictive value (PPV) (80.9% vs. 3.4%).

Lindquist et al 2020, conducted a retrospective study of 66,166 patients who received screening or diagnostic testing in Australia. Results demonstrated that the sensitivity of the first-trimester screening for detection of T21, T13, and T18 was 89.6% with a screen-positive rate of 2.9% and that the sensitivity of cfDNA for the same conditions was 100% with a screen-positive rate of 2.4% when no-call results were included as positive. There was no statistically significant difference in the rate of any major chromosomal abnormality detected on prenatal or postnatal diagnostic testing after a low-risk screening result.

Rolling Circle Replication Cell-Free Fetal DNA Screening (e.g., Vanadis NIPT)

Literature supporting the utility of rolling circle replication cfDNA screening is limited. Published studies include proof of concept, and validation studies that are limited by potential conflicts of interest among the authors.

Pooh and colleagues (2021) in an observational, prospective validation study (CRITO) of 1218 pregnant individuals, aimed to validate the accuracy of the Vanadis NIPT system by determining the causes and mechanisms of discrepancies between results of Vanadis screening and genetic test results. The mean maternal age was 36.2 (18-50) and participants were at 11 weeks gestation or greater. The PPV of T21, T18, and T13 were 93.55%, 88.46%, and 100%, respectively. There were ten false positive cases. In 90% of those, results of further placental examination demonstrated that in 75% of these false positive cases, placental mosaicism or a demised twin with aneuploidy was confirmed. The study was aimed at evaluating the test in a high-risk population. Therefore, the clinical utility for the general population remains unclear.

Copy Number Variants- Microdeletions

Tian et al (2023) conducted a retrospective analysis of 452 pregnancies who had previously undergone chromosomal microarray analysis following amniocentesis or chorionic villus sampling. Participants also had NIPT with microdeletion and microduplication analysis performed and compared the testing results. Several syndromes due to copy number variants were identified with sensitivities ranging from 33%-100%. Limitations of the study include the low number of overall confirmed cases, the absence of confidence intervals for sensitivity, and a lack of statistical reporting for other test characteristics such as specificity, PPV, NPV, and uncertain indications for testing.

Rose et al (2022), for the American College of Genetics and Genomics (ACMG) conducted a systematic review of NIPT using cfDNA in general-risk pregnancies. The study included 17 studies of screening for microdeletions and microduplications. Meta-analyses were not conducted due to study heterogeneity. Although screening identified a small number of copy number variants, confirmatory testing was frequently unavailable. The sample size of each study was small and sensitivities had great variation. Additionally, it was difficult to distinguish between low- and high-risk cohorts in

individual studies. The study authors concluded that the performance of NIPT was significantly poorer when targeting copy number variants than T21, T13, and T18, and additional outcome studies are needed to understand the unique clinical value of NIPT for copy number variants.

Zaninovic et al (2022) conducted a systematic review of NIPT for copy number variants and microdeletions. A total of 32 studies were identified with literature search conducted through February 2022. Of these, 21 studies concerned screening for microdeletion syndromes. Meta-analyses were not conducted due to study heterogeneity. The authors described important limitations of the included studies. Most studies did not define indications for screening and some included only high-risk pregnancies. Negative predictive values could not be determined because none of the studies performed systematic analysis confirming the outcome by chromosomal microarray analysis for negative/low-risk cases, most relied upon clinical follow-up. The study authors concluded that given the limited follow-up and validation data available, NIPT for microdeletions and copy number variants should be used with caution.

Multiple Gestations

Judah et al (2021) reported on cfDNA testing in 1,442 twin pregnancies. Study populations included a mix of high and average-risk pregnancies for aneuploidies. The cfDNA test classified correctly 19 (95.0%) of the 20 cases of T21, nine (90.0%) of ten cases of T18, one (50.0%) of two cases of T13, and 1,235 (99.6%) of 1,240 cases without any of the three trisomies. The pooled weighted detection rate and false positive rate (FPR) were 99.0% (95% CI 92.0% to 99.9%) and 0.02% (95% CI 0.001% to 0.43%), respectively. In the combined total of 50 cases of T18 and 6,840 non-trisomy 18 pregnancies, the pooled weighted detection rate and FPR were 92.8% (95% CI 77.6% to 98.0%) and 0.01% (95% CI 0.00, 0.44%), respectively. In the combined total of 11 cases of T13 and 6,290 non-trisomy 13 pregnancies, the pooled weighted detection rate and FPR were 94.7% (95% CI 9.14, 99.97%) and 0.10% (95% CI 0.03% to 0.39%). The evidence was limited by the small number of cases and individual study limitations included a high risk of selection bias (e.g., screening performed in populations that had previously been screened using methods including the pregnant individuals' age, first-trimester combined test, or second-trimester serum biochemistry). The study authors concluded that the detection rate of T21 was high, but lower than that in singleton pregnancies. The number of cases of T18 and T13 was too small for an accurate assessment of the predictive performance of the test.

The Rose et al (2022) study also reported performance characteristics of NIPT to detect trisomies in multifetal gestations. Seven studies representing 4,271 twin pregnancies were included in meta-analyses. The study authors concluded that performance characteristics were generally comparable to NIPT performance in singleton pregnancies but that few studies had comprehensively evaluated NIPT performance in twin gestations. In addition to the small number of cases overall, individual study limitations included a lack of complete follow-up data to be able to identify true negative and true positive cases, and an inability to distinguish low- and high-risk cohorts in some studies.

In 2022, the American College of Medical Genetics and Genomics (ACMG), based on the Rose et al systematic review, provided an updated guideline to their 2016 recommendations for NIPT for fetal chromosome abnormalities in a general-risk population. The update changed the societies' opinion regarding the use of NIPT for trisomy screening in twin gestations (strong recommendation, based on

high certainty of evidence), however, note that there are fewer published studies in existence compared to the number of studies in singleton pregnancies. The FASTER trial did not include twin pregnancies, and therefore, there is limited data on the performance of traditional screening in twin pregnancies (or higher-order multiples) for comparison.

The lack of direct evidence of the clinical utility of the use of cfDNA for multiple gestations is insufficient to determine that the technology results in an improvement in the net health outcome.

Twin Zygosity

Norwitz and colleagues (2019) conducted a prospective validation study of 126 total twin pregnancies using a single-nucleotide polymorphism-based NIPT. Of those evaluated, 95 samples with confirmed zygosity were available. Two samples had no results due to low fetal fraction. Of the 93 pregnancies with results, monozygotic sensitivity and specificity were 100%. The study had limitations. It is unknown if the samples were selected randomly or consecutively, and the techniques used to confirm zygosity varied. Future well-controlled studies are warranted to confirm the performance of the testing and determine how its use compares to standard care (early ultrasonographic confirmation).

Fetal Sex Chromosome Aneuploidy

The most common sex chromosome aneuploidy (SCA) is 47, XXY (Klinefelter syndrome), and has a prevalence of 1 in 500 males. The only viable monosomy is 45, X (Turner Syndrome) and has a prevalence of 1 in 2,500. Available data on the diagnostic performance of sequencing-based tests for detecting SCA is limited. The data available suggests its performance is not as high as it is for detection of T21, T18, and T13 and there is a higher rate of false-positive tests.

Badeau et al (2017), in a Cochrane review, evaluated the diagnostic accuracy of NIPT for SCA by reviewing 12 studies conducted on the 45, X chromosome with sensitivities of 91.7% to 92.4% and specificities of 99.6% to 99.8%. Reviewers calculated that of 100,000 pregnancies, 1,039 would be affected by 45, X chromosomes. Of these, 953 (massively parallel sequencing) and 960 (targeted massively parallel sequencing) would be detected, and 86 and 79 cases, respectively, would be missed. Of the 98,961 unaffected women, 396 and 198 pregnant women would undergo unnecessary invasive tests. The authors were unable to perform meta-analyses of NIPT for chromosomes 47, XXX, 47, XXY, and 47, XYY due to insufficient evidence.

ACMG's 2022 guideline update (based upon the systematic review by Roseet al 2022) included a changed opinion regarding the use of NIPT for fetal SCA. The society states that "The option of screening for fetal SCA is unique to NIP[T] and has not been available through traditional screening. Therefore, direct comparisons of screening performance between the two modalities cannot be done." ACMG notes that the performance of NIPT for SCA was high across all the common types (monosomy X, XXX, XXY, and XYY) with detection rates of 99.8% (95% CI=94.8-100%) and a specificity of 99.8% (95% CI=99.7%-99.9%) however, positive predictive values (PPV) differ across the SCAs. The PPVs for NIPT use for screening of 47, XXY, for example, was 74% (95% CI=58.4%-85.8%). The PPV for NIPT use for screening of 45, X was 29.5% (95% CI=22.7%-37.4%). Additionally, the studies that were reviewed by the panel did not specify the type of diagnostic testing performed to confirm SCA.

The current literature does not provide conclusive evidence that NIPT screening for SCA has a definite positive effect on health outcomes.

Single Gene Disorders

The performance of the UNITY single-gene NIPT was evaluated in a clinical validation study by Hoskovec et al in 2023. The study participants (n=9151) included a non-high risk general population for cystic fibrosis, hemoglobinopathies, and spinal muscular atrophy, who were screened with UNITY from August 2019 to May 2021. All pregnancies were singletons, greater than or equal to 10 weeks gestation and were not conceived with a donor egg or gestational carrier. A total of 1669 (18.2%) women within the cohort were found to be heterozygous carriers for a pathogenic variant of at least one condition (4.47% were heterozygous for a CFTR pathogenic variant, 4.64% for an HBB variant, 8.65% for HBA1/HBA2 variant, and 2.26% for SMN1) and underwent reflex single-gene NIPT. Newborn outcomes data was available for 201 (12%) pregnancies with an identified positive maternal carrier, and of these, 10 (4.9%) had no call single-gene NIPT results and were excluded from the analysis. Single-gene NIPT identified 14 out of 15 affected fetuses as high risk for one of the screened conditions on the panel, resulting in a sensitivity of 93.3% (95% CI, 68.1% to 99.8%), a PPV of 48.3% (95% CI, 36.1% to 60.1%) and an NPV of 99.4% (95% CI, 96% to 99.9%). Newborn outcomes by proprietary personalized fetal risk score across all screened conditions showed that 4 out of 4 (100%) pregnancies with greater than nine in 10 risk were affected, 8 out of 17 (47%) with risks between one in two and two in three risk were affected, two out of eight (25%) with risks between one in 10 and one in 100 were affected, and one out of 162 (0.6%) with risks less than one in 100 were affected. The authors modeled the end-to-end clinical analytics of carrier screening with UNITY versus standard NGS carrier screening. The authors reported that in a real-world scenario accounting for the sensitivity of carrier screening and single-gene NIPT, the end-to-end sensitivity of carrier screening with UNITY was 90% (95% CI, 71.8% to 98.9%), which was higher than that for conventional carrier screening. Wynn et al (2023) also evaluated the UNITY NIPT in a general population of 42,067 pregnant individuals who underwent UNITY carrier screening. A total of 7538 (17.92%) carriers were identified and underwent reflex single-gene NIPT. Only 3299 were able to be contacted for follow-up. The outcomes cohort consisted of 528 neonates and fetuses who were able to be assessed for single-gene disorders across 253 centers in the U.S. The authors calculated that in this cohort, the sensitivity of the UNITY NIPT was 96.0% (95% CI, 79.65% to 99.90%), with a specificity of 95.2% (95% CI, 92.98%to 96.92%), PPV of 50.0% (95% CI, 35.23% to 64.77%), and an NPV of 99.8% (95% CI, 98.84% to 99.99%). Single-gene NIPT identified nine of 10 pregnancies affected by cystic fibrosis, 11 of 11 affected HBB, four of four affected by spinal muscular atrophy, and none affected by HBA as high risk. The authors modeled the performance characteristics of maternal carrier screening followed by single-gene NIPT with the UNITY NIPT. They found an end-to-end sensitivity of 92.4% with a specificity of 99.9% and PPV and NPV values of 50.7% and 99.9%, respectively of the full cohort of 42067 pregnancies; this was higher than conventional carrier screening and would result in a greater number of fetuses being characterized as high risk. There are major limitations to these studies including data, a lack of consistent confirmatory testing methods, and selection bias. Given the limitations, it is not possible to determine accurate estimates of true positive and true negative tests. The added benefit of Unity NIPT compared with current approaches is unclear.

Wynn et al (2023) also evaluated the use of carrier screening with reflex to single-gene noninvasive prenatal testing (UNITY Fetal Risk Screen) as an alternative approach for identifying pregnancies at risk for inherited autosomal recessive conditions without the need for a sample from the reproductive partner. Of 42,067 pregnant individuals who underwent screening, 7538 carriers (17.9%) had reflex sgNIPT, and neonatal or fetal outcomes were obtained for 528 cases, including 25 affected pregnancies. The authors calculated that in this cohort, the sensitivity of the UNITY Fetal Risk Screen was 96.0% (95% CI, 79.65% to 99.90%), with a specificity of 95.2% (95% CI, 92.98%to 96.92%), PPV of 50.0% (95% CI, 35.23% to 64.77%), and an NPV of 99.8% (95% CI, 98.84% to 99.99%). Single-gene NIPT identified 9 of 10 pregnancies affected by cystic fibrosis, 11 of 11 affected HBB, 4 of 4 affected by spinal muscular atrophy, and none affected by HBA as high risk. The authors also modeled the performance characteristics of maternal carrier screening followed by single-gene NIPT with the UNITY Fetal Risk Screen. They found an end-to-end sensitivity of 92.4% with a specificity of 99.9% and PPV and NPV values of 50.7% and 99.9%, respectively of the full cohort of 42067 pregnancies; this was higher than conventional carrier screening and would result in a greater number of fetuses being characterized as high risk. There is a potential that prenatal identification of pregnancies with single-gene disorders could improve health outcomes to allow for informed reproductive decision-making as well as initiate earlier treatment; however, data demonstrating improvement are unavailable. Major limitations include missing data, a lack of consistent confirmatory testing methods, and selection bias**.** Additionally, given the variability of single-gene disorders identified by the tests, there is a lack of experience with routine genetic screening for some of these disorders, with uncertainty regarding clinical decision-making based on the NIPT results. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Fetal RhD

For individuals who are pregnant and have Rhesus D (RhD)-negative blood type who receive noninvasive RhD genotyping of the fetus using cfDNA from maternal plasma, the evidence includes two meta-analyses and additional prospective studies and one retrospective cohort for clinical utility. Relevant outcomes are test validity, morbid events, medication use, and treatment-related morbidity. Clinical validity studies have demonstrated that the sensitivity of both currently available tests are 100% and the specificity of both tests is very high (99.3% to 100%). Prospective studies comparing outcomes in patients managed with and without the test are lacking. The evidence is sufficient to determine that this technology results in an improvement in the net health outcomes.

A 2020 Ontario Health Technology Assessment (HTA) evaluated the accuracy, clinical utility, and cost-effectiveness of noninvasive fetal RhD blood group genotyping for RhD-negative pregnant individuals. The evaluation included a literature search which identified six systematic reviews addressing test accuracy and eleven studies addressing clinical utility. Test accuracy was found to be high across all the systematic reviews and indicated that implementation of fetal cfDNA testing for RhD genotype could lead to avoidance of unneeded RhIG prophylaxis (GRADE: Low), good compliance with targeted RHIG prophylaxis (GRADE: very low), and high uptake of genotyping (GRADE: low). In addition, alloimmunization may not increase with the use of fetal cfDNA RhD genotyping for targeting prenatal RhIG prophylaxis and unnecessary monitoring and invasive procedures in alloimmunized pregnant individuals may be reduced (both GRADE: very low). The HTA

concluded that overall, fetal cfDNA testing for fetal RhD blood group genotyping is an accurate test to detect RhD incompatibility and help steer management of RhD-negative pregnancies.

A prospective cohort, systematic review and meta-analysis was performed by Yang et al (2019, included in the 2020 Ontario HTA discussed above) to assess the diagnostic accuracy of high-throughput NIPT for fetal RhD status in RhD-negative women not known to be sensitized to the RhD antigen. Databases scanned for this meta-analysis included MEDLINE, EMBASE and Science Citation Index and were searched through February 2016. Included for review were 3,921 identified studies. The study population included RhD negative pregnant women known to not be sensitized to the RhD antigen and the index test was high throughput cfDNA on maternal plasma. Serological cord blood testing at birth was considered the reference standard and eligible studies were required to report diagnostic accuracy data including true positive, false positive, true negative and false negative absolute numbers. Diagnostic accuracy of NIPT varied by gestational age with data suggesting that NIPT was consistently accurate any time after the first trimester. The false negative rate (those incorrectly classified as RhD negative) was 0.34% (95% CI 0.15-0.76) and the false positive rate (incorrectly classified as RhD positive) was 3.86% (95% CI 2.54-5.82). Because this study is a meta-analysis, the authors described the risk of bias in the original articles and several of the included studies were deemed to be high-risk for bias due to the selected populations and the reference standards. Authors concluded, the use of high-throughput NIPT testing as a routine screening test for fetal RhD status in RhD-negative women can largely remove unnecessary exposure to prophylactic anti-D treatment (Anti-D (rh) immunoglobulin is a prescription medication used to prevent Rh immunization, also known as Rh incompatibility).

A clinical validation study was performed by Thompson, et al (2025) that aimed to provide clinical validation of NGS-based, noninvasive prenatal cfDNA test for fetal RhD (Natera). 655 pregnant patients with RhD-negative serology were used in this study. At the time of analysis, investigators were blinded to fetal RhD status. There were zero false-negative cases; 356 of 356 fetuses were correctly identified as fetal RhD positive (sensitivity 100%, 95% CI, 98.9–100%). Of the 297 RhD-negative fetuses, 295 were correctly identified as RhD negative (specificity 99.3%, 95% CI, 97.6–99.8%). Authors concluded that this test has the potential to assist patients and clinicians in the prevention and management of RhD alloimmunization.

Mustafa et a (2025) published a systematic review and meta-analysis that aimed to evaluate the diagnostic accuracy of cell-free DNA in identifying fetal red blood cell antigen genotypes. A total of 84 cohort studies (77 prospective and 7 retrospective) were evaluated. Alloimmunized pregnancies were included in 10 studies, non-alloimmunized pregnancies were included in 66 studies, and a combination of alloimmunized and non-alloimmunized pregnancies were included in 8 studies. A total of 77,187 fetal antigen samples were evaluated in the included studies. Several laboratory methods were used including polymerase chain reaction, next-generation sequencing, and matrix-assisted laser desorption/ionization-time of flight. Overall, the sensitivity and specificity of cffDNA were 99% and 99%, respectively.

PROFESSIONAL GUIDELINE(S)

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

(SMFM) addressed screening for fetal chromosomal abnormalities in ACOG Practice Bulletin Number 226 (2020).

Level A recommendations (based on good and consistent scientific evidence) regarding cfDNA include:

- Prenatal genetic screening (serum screening with or without nuchal translucency ultrasound or cfDNA screening) and diagnostic testing should be offered to all pregnant women regardless of maternal age or risk for chromosome abnormality.
- If screening is accepted, patients should only have one screening performed and not multiple screening tests performed simultaneously.
- cfDNA 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, cfDNA testing is not equivalent to diagnostic testing.
- Patients with positive screening should have genetic counseling, comprehensive ultrasound and be offered diagnostic testing.
- Patients whose cfDNA are not reportable are at increased risk for chromosomal aneuploidy and should be offered genetic counseling, comprehensive ultrasound, and diagnostic testing.

Level B recommendations (based on limited or inconsistent scientific evidence) regarding cfDNA include:

- The use of cfDNA as follow-up for patients with a screen positive serum-analyte test result is an option for patients who want to avoid diagnostic testing.
- In situations of isolated soft ultrasound markers and no prior screening has been performed either cfDNA, quad screen or diagnostic testing should be offered.
- cfDNA screening can be performed for twin pregnancies. Overall performance of screening for trisomy 21 by cfDNA 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.
- Prenatal screening and prenatal diagnosis should be offered to all pregnant individuals regardless of previous preimplantation genetic testing.

Level C recommendations (primarily based on consensus/expert opinion) regarding cfDNA include:

- 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 cfDNA is used. In these situations, the pregnant individual should be counseled on this information and offered diagnostic testing.
- Patients with unusual or multiple aneuploidies detected by cfDNA should be referred to genetic counseling.

In 2024, the ACOG reaffirmed its 2006 position (Practice bulletin 192) that detection of fetal Rhesus D (RhD) using molecular analysis of maternal plasma or serum can be assessed in the second trimester with an accuracy greater than 99%; however, this test is not a widely used clinical tool.

ACOG has recommended that the first dose of Rh(D) immunoglobulin (e.g., RhoGAM) be given at 28 weeks of gestation (or earlier if there's been an invasive event), followed by a postpartum dose given within 72 hours of delivery. This statement was last reaffirmed in 2024.

In its 2017 Practice Bulletin Number 181 on the prevention of RhD alloimmunization, the College stated that "Despite the improved accuracies noted with noninvasive fetal RhD genotyping, cost comparisons with current routine prophylaxis of anti-D immunoglobulin at 28 weeks of gestation have not shown a consistent benefit and, thus, this test is not routinely recommended." This statement was last reaffirmed in 2024.

Sperling et al (2018) compared the guidelines from the American College of Obstetricians and Gynecologists as well as 3 international guidelines on the prevention of RhD alloimmunization. All four guidelines recommended that all women have an antibody screen with an indirect Coombs test at prenatal intake and at 24 to 28 weeks. None currently recommend screening with cfDNA.

An ACOG practice advisory recognizes the emerging technology and availability of cfDNA screening for single-gene disorders but emphasized that there is insufficient evidence to demonstrate accuracy and positive and negative predictive values for general population use (ACOG, 2019; reaffirmed 2024). For this reason, ACOG does not recommend single gene cfDNA screening in pregnancy.

Another ACOG practice advisory addressing the Rho(D) Immune Globulin Shortages (July 2024; reaffirmed March 2025) states that although current ACOG guidance does not recommend routine use of noninvasive prenatal testing (NIPT) to determine fetal Rh(D) status based on cost-effectiveness analyses, the use of NIPT to prioritize use of RhIg and conserve RhIg supply is a reasonable consideration in the practice setting that is experiencing RhIg shortages. Noninvasive fetal red blood cell antigen genotyping utilizing cell-free DNA (cfDNA) isolated from maternal plasma has demonstrated high sensitivity and specificity for detection of fetal Rh(D) antigen status. If cfDNA testing results confirm an Rh(D)-negative fetus, RhIg would not need to be routinely administered in the antepartum period (for bleeding, abortion, pregnancy loss, or at 28 weeks of gestation).

A Clinical Practice Update by Miller et al (2024) updated ACOG Practice Bulletin 192, Management of Alloimmunization in Pregnancy by clarifying guidance on paternal genotyping and provided new recommendations on the role of non-invasive fetal red blood cells antigen genotyping using cell-free DNA. The updated guidelines provided the following recommendations:

- Paternal RHD zygosity testing using genotypic analysis is recommended for Rh-D alloimmunization risk assessment. It may be reasonable to defer or fetal surveillance for anemia in the setting of paternal genotyping that is RHD homozygous negative.
- Because cfDNA testing possesses performance characteristics that appear comparable with those of molecular testing, while avoiding the rare complications and costs associated with diagnostic genetic testing, it is reasonable to use it as an alternative tool for fetal RHD testing among allo-immunized patients with potentially at-risk pregnancies who decline amniocentesis.
- Cell-free DNA for the assessment of selected non–Rh-D red blood cell antigens may be considered for pregnant patients declining amniocentesis, after weighing cost, access, and the encouraging-yet-limited data supporting its use.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing.

More information is available at:
Clinical Laboratory Improvement Amendments (CLIA) | FDA [accessed2026 Feb 5]

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
76813	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation (only in conjunction with 84163/84704).
76814	Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; each additional gestation (List separately in addition to code for primary procedure) (only in conjunction with 84163 /84704).
81420	Fetal chromosomal aneuploidy (e.g., trisomy 21, monosomy X), genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosome 13, 18, and 21
81422 (E/I)	Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
81479 (*E/I)	Unlisted molecular pathology procedure (e.g., Vanadis NIPT) (*E/I Refer to Policy Statement VI.F.)
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
81599 (*E/I)	Unlisted multianalyte assay with algorithmic analysis (e.g., sex chromosome aneuploidy) (*E/I Refer to Policy Statement VI.D.)

Code	Description
84163	Pregnancy-associated plasma protein-A (PAPP-A)
84704	Gonadotropin, chorionic (hCG); free beta chain
0060U (NMN)	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood (Twin Zygosity PLA, Natera, Inc)
0327U (E/I)	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed. (Vasistera, Natera, Inc)
0489U (*E/I)	Obstetrics (single-gene noninvasive prenatal test), cell-free DNA sequence analysis of 1 or more targets (e.g., CFTR, SMN1, HBB, HBA1, HBA2) to identify paternally inherited pathogenic variants, and relative mutation-dosage analysis based on molecular counts to determine fetal inheritance of maternal mutation, algorithm reported as a fetal risk score for the condition (e.g., cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia) (Unity Fetal Risk Screen, Billion To One) (*E/I Refer to Policy Statement VI.E)
0494U	Red blood cell antigen (fetal RhD gene analysis), next-generation sequencing of circulating cell-free DNA (cfDNA) of blood in pregnant individuals known to be RhD negative, reported as positive or negative (Rh Test, Natera)
0536U	Red blood cell antigen (fetal RhD), PCR analysis of exon 4 of RHD gene and housekeeping control gene GAPDH from whole blood in pregnant individuals at 10+ weeks gestation known to be RhD negative, reported as fetal RhD status (Prenatal Detect RhD, Devyser Genomic Laboratories, Devyser AB)

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
Q90.0-Q90.9	Down syndrome (code range)
Q91.0-Q91.7	Trisomy 18 and Trisomy 13 (code range)
Q92.0-Q92.5	Other trisomies and partial trisomies of the autosomes, not elsewhere classified (code range)

Code	Description
Q92.61-Q92.9	Marker Chromosomes (code range)
Q93.0-Q93.9	Monosomies and deletions from the autosomes, not elsewhere classified (code range)
Q95.0-Q95.9	Balanced rearrangements and structural markers, not elsewhere classified (code range)
Q96.0-Q96.9	Turner's syndrome (code range)
Q97.0-Q97.9	Other sex chromosome abnormalities, female phenotype, not elsewhere classified
Q98.0-Q98.9	Other sex chromosome abnormalities, male phenotype, not elsewhere classified (code range)
Q99.0-Q99.9	Other chromosome abnormalities, not elsewhere classified (code range)
Z31.430-Z31.448	Encounter for procreative investigation and testing, male or female (code range)
Z31.5	Encounter for procreative genetic counseling
Z36.0-Z36.9	Encounter for antenatal screening of mother (code range)

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

There is currently no National Coverage Determination (NCD) or Local Coverage Determination (LCD) for First Trimester Screening of Down Syndrome. However, CMS considers HCG testing a covered indication in specific instances but is not addressed in relation to first trimester screening for Down syndrome.

LCD - Molecular Pathology Procedures (L35000) [accessed 2026 Mar 12]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates

11/18/04, 09/15/05, 07/20/06, 08/16/07, 08/21/08, 02/19/09, 04/21/11, 03/15/12, 03/21/13, 06/20/13, 07/17/14, 03/19/15, 03/17/16, 06/15/17, 03/15/18, 03/21/19, 03/19/20, 03/18/21, 03/24/22, 05/18/23, 04/18/24, 04/17/25, 04/16/26

Date	Summary of Changes
05/13/26	• Policy edit; Vasistera removed as an example for single-gene disorders testing. Vasistera is considered a limited NIPT for common chromosomal aneuploidies and is investigational.
04/16/26	• Annual review. The policy stance for measurement of cell-free DNA for fetal genotyping for RhD antigen was updated from an investigational stance to medically appropriate when specific criteria is met. Additions to policy include reference to CMP# 4.01.03 as well as Canned Genetic Testing Policy Guidelines. PLA code 0449U has been removed and relocated to CMP#4.01.03.
04/17/25	• Annual review. Addition of RhD criteria as investigational. New CPT code 0536U added.

01/01/25	• Summary of changes tracking implemented.
11/18/04	• Original effective date