

# MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	Non-Invasive-Prenatal Testing
Policy Number	02.02.25
Category	Technology Assessment
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Archive Review Date	N/A
Product Disclaimer	<ul style="list-style-type: none"> <li>Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</li> <li>If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.</li> <li>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.</li> <li>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.</li> <li>If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.</li> </ul>

## POLICY STATEMENT

- I. Based upon our criteria and assessment of the peer-reviewed literature, noninvasive 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 considered **medically appropriate** for those members with singleton pregnancies.
- II. Based upon our criteria and assessment of the peer-reviewed literature, 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. Based upon our criteria and assessment of the peer-reviewed literature, screening for detection of chromosomal abnormalities using measurement of nuchal translucency alone has not been proven to be effective and, therefore, is considered **not medically necessary**.
- IV. Based upon our criteria and assessment of the peer-reviewed literature, (NIPT) for the determination of twin zygosity does not improve patient outcomes and, therefore, is considered **not medically necessary** (CPT: 0060U).
- V. Based upon our criteria and assessment of the peer-reviewed literature, NIPT has not been medically proven to be effective and, therefore, is considered **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);

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- D. fetal sex chromosome aneuploidy (SCA);
- E. single-gene disorder screening (e.g., Vistara [Natera], Unity Screen [Billion To One])
- F. Rolling circle replication cell-free fetal DNA screening (e.g., Vanadis NIPT);
- G. Measurement of fetal nasal bone length.

*Refer to Corporate Medical Policy #2.02.03 Genetic Testing for Inherited Disorders*

*Refer to Corporate Medical Policy #4.01.03 Prenatal Genetic Testing*

*Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services*

### **POLICY GUIDELINE**

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.

### **DESCRIPTION**

The American College of Obstetricians and Gynecologists (ACOG, 2020) recommends that all pregnant patients be offered screening for chromosomal abnormalities regardless of age at pregnancy or risk (Recommendation level A).

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/99<sup>th</sup> 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.

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### 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) (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.

To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of NIPT using cfDNA. Commercially available tests include but are not limited to: Myriad Prequel Prenatal Screen (Myriad Women's Health, Counsyl), VisibiliT (Sequenom Laboratories, now LabCorp), MaterniT21 PLUS (Sequenom Laboratories, now LabCorp), Harmony (Ariosa Diagnostics, now Roche), Panorama (Natera), Verifi (Verinata Health, now Illumina), InformSeq (Integrated Genetics, now LabCorp), QNatal Advanced (Quest Diagnostics), Vanadis NIPT Solution (Perkin Elmer), Veracity (NIPD Genetics), Vistara Single-Gene NIPT test (Natera), Unity (Billion to One).

### 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-Hirschhorn 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. The Vistara Single-Gene NIPT panel (Natera) is a blood sample screening for 25 conditions that result from variants in 30 genes which have a combined prevalence of 1 in 600. 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 a priori risk factors to establish a proprietary personalized fetal risk score

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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 monozygotic (identical) twin pregnancies share their blood supply. Monozygotic 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 monozygotic 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 monozygotic twin pregnancies. In these twin pregnancies, fetal ultrasound examinations are necessary to monitor for 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 monozygotic 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.

## **RATIONALE**

### 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  $\beta$ -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.

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### 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.

### 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.

The American College of Obstetricians and Gynecologists (ACOG, 2020) recommends that when a patient elects screening for aneuploidy, only one screening approach should be used. "Analyte screening and cell-free DNA screening should not be sent concurrently as this strategy is not cost-effective and simultaneous, seemingly discordant results can be more distressing to patients than screen positive analyte results followed by reassuring cell-free DNA screening."

### 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 to evaluate 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.

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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. Sample sizes in each study were 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 searches 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 on 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.

ACOG (2020), in their Practice Bulletin for Fetal Chromosomal Abnormalities, agrees that screening for a limited number of microdeletions with cfDNA is available, but it has not been validated clinically and is not recommended, also noting that microdeletions, although relatively common when they are viewed in total, the existing panels only include a few specific microdeletions that are very rare, and therefore, the positive predictive value is much lower than T21, T13 and T18.

### Multiple Gestations

The most recent guidance on NIPT for multiple gestations from ACOG (2020) states that the use of cfDNA screening can be performed in twin gestations and that its performance for T21 is encouraging, however, the total number of affected cases that are reported is small (Level B recommendation). Masking of an aneuploid test result may occur in twin pregnancies because an aneuploid fetus would contribute less fetal DNA. Even though recent studies have shown that the sensitivity in twin pregnancies for trisomy 21 may be similar to singletons, there is a higher rate of test failure.

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.

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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 Rose, et 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 literature available for the use of Vistara Single-gene NIPT includes retrospective cohort studies (Zhang, 2019) and Mohen, 2022) and have a concern for multiple limitations, including a lack of confirmatory testing, missing follow-up data and potential for selection bias, which creates difficulty with determining accurate estimates of true positive and true negative results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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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 a 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.

There is a potential that prenatal identification of pregnancies with single-gene disorders could improve health outcomes to allow for informed reproductive decision-making and/or initiate earlier treatment; however, data demonstrating improvement are unavailable. 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.

### **CODES**

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- ***CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.***
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/appropriate = (NMN).*



**Medical Policy: NON-INVASIVE PRENATAL TESTING****Policy Number: 02.02.25****Page: 9 of 12****CPT Codes**

<b>Code</b>	<b>Description</b>
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	Unlisted molecular pathology procedure (e.g., Vanadis NIPT) <b>(E/I) Refer to Policy Statement V.F.</b>
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	Unlisted multianalyte assay with algorithmic analysis (e.g., sex chromosome aneuploidy) <b>(E/I) Refer to Policy Statement V.D.</b>
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. (Vistara, Natera, Inc)
0449U (E/I)	Carrier screening for severe inherited conditions (e.g., cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2) (Unity Screen, Billion To One) <i>(Effective 04/01/24)</i>

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**HCPCS Codes**

<b>Code</b>	<b>Description</b>
	No specific code(s)

**Medical Policy: NON-INVASIVE PRENATAL TESTING****Policy Number: 02.02.25****Page: 10 of 12****ICD10 Codes**

<b>Code</b>	<b>Description</b>
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)
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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### **KEY WORDS**

Nuchal translucency, free beta PAPP-A, PAPP-A, cell-free fetal DNA, noninvasive prenatal testing, MaterniT21, Verify, Harmony, Panorama, Vanadis, Vistara, Unity, prenatal testing for single-gene disorders, twin-zygosity.

### **CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS**

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.

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures (L35000) which includes the CPT codes for Noninvasive Prenatal Testing. Please refer to the following LCD website for Medicare members:

[https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=140&ContrId=298&ContrVer=1&CntrctrSelected=298\\*1&Cntrctr=298&s=41&DocType=1&bc=AIIAAACAAAA&=](https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35000&ver=140&ContrId=298&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AIIAAACAAAA&=) accessed 03/04/24.