Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions, Single-Gene Disorders, and Twin Zygosity Using Cell-Free Fetal DNA

Policy # 00345
Original Effective Date: 12/20/2013
Current Effective Date: 05/01/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies is addressed separately in medical policy 00536.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider nucleic acid sequencing-based testing of maternal plasma to screen for trisomy 21, 18, and 13 in individuals with single or twin gestation pregnancy (except as noted below) to be **eligible for coverage.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma to screen for trisomy 21, 18, and 13 in individuals with twin pregnancy affected by fetal demise or vanishing twin, and pregnancies involving three or more fetuses to be **investigational.***

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Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma in all other situations, including more than one prenatal cell-free DNA test per pregnancy, to be **investigational.***

Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma for fetal sex chromosome aneuploidies to be **investigational.***

Note:
Screening for aneuploidy of the X and Y chromosome and/or detection of less common trisomies are not separately reimbursable; additional procedure codes billed with cell-free DNA screening for this purpose are not eligible for reimbursement.

Based on review of available data, the Company considers nucleic acid sequencing-based testing of maternal plasma for microdeletions and twin zygosity to be **investigational.***

Based on review of available data, the Company considers Vanadis NIPT of maternal plasma to screen for trisomy 21, 18 and 13 in all situations to be **investigational.***

Based on review of available data, the Company considers Vistara NIPT of maternal plasma to screen for single-gene disorders in all situations to be **investigational.***

Based on review of available data, the Company considers single cell genotyping in trophoblasts isolated from maternal serum (e.g., Luna Prenatal Test) to be **investigational.***

Policy Guidelines

Nucleic acid sequencing-based testing (noninvasive prenatal testing or NIPT) is also referred to as cell-free fetal DNA (cffDNA) testing.

Karyotyping would be necessary to exclude the possibility of a false-positive, nucleic acid sequencing-based test. Before testing, women individuals should be counseled about the risk of a false-positive test. In Committee Opinion No. 640, the American College of Obstetricians and Gynecologists (2015) recommended that all patients receive information on the risks and benefits of

various methods of prenatal screening and diagnostic testing for fetal aneuploidies, including the option of no testing.

Studies published to date on noninvasive prenatal screening for fetal aneuploidies have reported rare but occasional false-positives. False-positive findings have been found to be associated with factors including placental mosaicism, vanishing twins, and maternal malignancies. Diagnostic testing is necessary to confirm positive cell-free fetal DNA tests, and management decisions should not be based solely on the results of cell-free fetal DNA testing. The American College of Obstetricians and Gynecologists further recommended that individuals with indeterminate or uninterpretable (ie, "no call") cell-free fetal DNA test results be referred for genetic counseling and offered ultrasound evaluation and diagnostic testing because "no-call" findings have been associated with an increased risk of aneuploidy.

Cell-free fetal DNA screening does not assess the risk of neural tube defects. Individuals should continue to be offered ultrasound or maternal serum alpha-fetoprotein screening.

Background/Overview

Fetal Aneuploidy

Fetal chromosomal abnormalities occur in approximately 1 in 160 live births. Most fetal chromosomal abnormalities are aneuploidies, defined as an abnormal number of chromosomes. The trisomy syndromes are aneuploidies involving 3 copies of 1 chromosome. The most important risk factor for trisomy syndromes is maternal age. The approximate risk of a trisomy 21 (T21; Down syndrome)-affected birth is 1 in 1100 at age 25 to 29. The risk of a fetus with T21 (at 16 weeks of gestation) is about 1 in 250 at age 35 and 1 in 75 at age 40.

Trisomy 21 is the most common chromosomal aneuploidy. Other trisomy syndromes include T18 (Edwards syndrome) and T13 (Patau syndrome), which are the next most common forms of fetal aneuploidy, although the percentage of cases surviving to birth is low, and survival beyond birth is limited. Detection of T18 and T13 early in pregnancy can facilitate preparation for fetal loss or early intervention.

Fetal Aneuploidy Screening

Standard aneuploidy screening involves combinations of maternal serum markers and fetal ultrasound done at various stages of pregnancy. The detection rate for various combinations of noninvasive testing ranges from 60% to 96% when the false-positive rate is set at 5%. When tests indicate a high risk of a trisomy syndrome, direct karyotyping of fetal tissue obtained by amniocentesis or chorionic villous sampling is required to confirm that T21 or another trisomy is present. Both amniocentesis and chronic villous sampling are invasive procedures and have procedure-associated risks of fetal injury, fetal loss, and infection. A new screening strategy that reduces unnecessary amniocentesis and chorionic villous sampling procedures or increases detection of T21, T18, and T13 could improve outcomes. Confirmation of positive noninvasive screening tests with amniocentesis or chronic villous sampling is recommended. Amniocentesis might be preferred over chorionic villus sampling for confirming cell-free DNA positive results due to the potential for placental mosaicism leading to false positive results. With more accurate screening tests, fewer individuals would receive positive screening results.

Commercial, noninvasive, sequencing-based testing of maternal serum for fetal trisomy syndromes is now available. The testing technology involves the detection of cell-free fetal DNA fragments present in the plasma of pregnant women. As early as 8 to 10 weeks of gestation, these fetal DNA fragments comprise 6% to 10% or more of the total cell-free fetal DNA in a maternal plasma sample. The tests are unable to provide a result if the fetal fraction is too low (ie, <4%). The fetal fraction can be affected by maternal and fetal characteristics. For example, the fetal fraction was found to be lower at higher maternal weights and higher with increasing fetal crown-rump length.

Twin Zygosity Testing

Twin gestations occur in approximately 1 in 30 live births in the United States and have a 4- to 10-fold increased risk of perinatal complications. Dizygotic or "fraternal" twins occur from ovulation and fertilization of 2 oocytes, which results in dichorionic placentation and 2 separate placentas. In contrast to dichorionic twins, monochorionic 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 relative hypovolemia of 1 twin and hypervolemia of the other. According to estimates from live births, TTTS occurs in up to 15% of monochorionic

twin pregnancies. In these twin pregnancies, serial 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 are amenable to interventions that can improve outcomes. Noninvasive prenatal testing (NIPT) using cell-free fetal DNA to determine zygosity in twin pregnancies could potentially inform decisions about early surveillance for TTTS and other monochorionic twin-related abnormalities. In particular, determining zygosity with NIPT could potentially assist in the assessment of chorionicity when ultrasound findings are not clear.

Single-Gene Disorders

Single-gene disorders (also known as monogenic disorders) are caused by a variation in a single gene. Individually, single-gene disorders are rare, but collectively are present in approximately 1% of births. The Vistara Single-Gene Disorder Test panel screens for 25 conditions that result from variants across 30 genes, which have a combined incidence of 1 in 600 (0.17%).These include 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. The clinical presentation and severity of these disorders can vary widely. Some, but not all, can be detected by prenatal ultrasound examination.

Cell-Free Fetal DNA Analysis Methods

Sequencing-based tests use 1 of 2 general approaches to analyzing cell-free fetal DNA. The first category of tests uses quantitative or counting methods. The most widely used technique to date uses massively parallel sequencing (MPS; also known as next-generation sequencing). DNA fragments are amplified by polymerase chain reaction; during the sequencing process, the amplified fragments are spatially segregated and sequenced simultaneously in a massively parallel fashion. Sequenced fragments can be mapped to the reference human genome to obtain numbers of fragment counts per chromosome. The sequencing-derived percent of fragments from the chromosome of interest reflects the chromosomal representation of the maternal and fetal DNA fragments in the original maternal plasma sample. Another technique is direct DNA analysis, which analyzes specific cell-free fetal DNA fragments across samples and requires approximately a tenth the number of cell-free DNA fragments as MPS. The digital analysis of selected regions (DANSR™‡) is an assay that uses direct DNA analysis.

The second general approach is single nucleotide variant-based methods. They use targeted amplification and analysis of approximately 20,000 single nucleotide variants on selected chromosomes (eg, 21, 18, 13) in a single reaction. A statistical algorithm is used to determine the number of each type of chromosome. At least some of the commercially available cell-free fetal DNA prenatal tests also test for other abnormalities including sex chromosome abnormalities and selected microdeletions.

A newer approach to cell-free DNA testing called the Vanadis NIPT does not involve polymerase chain reaction (PCR) amplification or sequencing. The procedure consists of the digestion of cell-free DNA (cfDNA) using a restriction enzyme. The digested cfDNA is then hybridized and ligated to chromosome-specific DNA probes forming a circular DNA. All non-circular DNA is removed by exonuclease treatment. Finally, the circular DNA containing the cfDNA is amplified with rolling circle amplification to form rolling circle products that are labeled with chromosome-specific fluorescently labeled DNA probes. The fluorescently labeled rolling circle products are imaged and counted with an automated microscopy scanner. The microscope takes multiple images from each well with different spectral filters, ie each wavelength range presents a specific chromosome. With image analysis algorithms, the fluorescently labeled rolling circle products are counted for each sample. The ratio between the number of chromosome-specific rolling circle products is then transferred to risk calculation software to calculate the likelihood of a trisomy. Currently, Vanadis NIPT provides results for trisomy 21, trisomy 18 and trisomy 13, and fetal sex determination.

Copy Number Variants and Clinical Disorders

Microdeletions (also known as submicroscopic deletions) are chromosomal deletions that are too small to be detected by microscopy or conventional cytogenetic methods. They can be as small as 1 and 3 megabases long. Along with microduplications, microdeletions are collectively known as copy number variants. Copy number variants can lead to disease when the change in the copy number of a dose-sensitive gene or genes disrupts the ability of the gene(s) to function and affects the amount of protein produced. A number of genomic disorders associated with microdeletion have been identified, which may be associated with serious clinical features, such as cardiac anomalies, immune deficiency, palatal defects, and developmental delay as in DiGeorge syndrome. Some of the syndromes (eg, DiGeorge) have complete penetrance yet marked variability in clinical expressivity. A contributing factor is that the breakpoints of the microdeletions may vary, and there may be a correlation between the number of haplo-insufficient genes and phenotypic severity.

A proportion of microdeletions are inherited and some are de novo. Accurate estimates of the prevalence of microdeletion syndromes during pregnancy or at birth are not available. The risk of a fetus with a microdeletion syndrome is independent of maternal age. There are few population-based data and most studies published to date have based estimates on phenotypic presentation. The 22q11.2 (DiGeorge) microdeletion is the most common associated with a clinical syndrome. Table 1 provides prevalence estimates for the most common microdeletion syndromes. These numbers likely underestimate the prevalence of these syndromes in the prenatal population because the population of variant carriers includes phenotypically normal or very mildly affected individuals.

Table 1. Recurrent Microdeletion Syndromes

Syndrome	Location	Estimated Prevalence
DiGeorge	22q11.2	1/2000
1p36 deletion	1p36-	1/5000
Prader-Willi and Angelman	Del 15q11.2	1/20,000
Wolf-Hirschhorn	4p-	1/50,000 to 1/20,000
Cri du chat	5p-	1/50,000
Miller-Dieker	Del 17p13.3	1 /100,000

Adapted from Chitty et al (2018).

Routine prenatal screening for microdeletion syndromes is not recommended by national organizations. Current practice is to offer invasive prenatal diagnostic testing in select cases to women when a prenatal ultrasound indicates anomalies (eg, heart defects, cleft palate) that could be associated with a particular microdeletion syndrome. For those who do have prenatal screening for microdeletion syndromes, diagnostic testing is necessary to confirm positive results. Diagnostic testing is generally done by chorionic villus sampling (cvs) or amniocentesis. CVS uses placental cells collected for genetic evaluation under ultrasound guidance without entering the amniotic sac. Diagnostic amniocentesis uses a small sample of the fluid that surrounds the fetus, which contains cells that are shed primarily from the fetal skin, bladder, gastrointestinal tract, and amnion. Confined placental mosaicism can cause false-positive cell-free DNA results, and as such, amniocentesis

might be preferred over CVS for diagnostic testing in cases of positive cell-free DNA. Both CVS and amniocentesis procedures increase the risk for miscarriage.

Samples are analyzed using fluorescence in situ hybridization, chromosomal microarray analysis, or karyotyping. Additionally, families at risk (eg, those known to have the deletion or with a previously affected child) generally receive genetic counseling, and those who conceive naturally may choose prenatal diagnostic testing. Most affected individuals, though, are identified postnatally based on clinical presentation and may be confirmed by genetic testing. Using 22q11.2 deletion syndrome as an example, although clinical characteristics vary, palatal abnormalities (eg, cleft palate) occur in approximately 69% of individuals, congenital heart disease in 74%, and characteristic facial features are present in a majority of individuals of northern European heritage.

Testing of Trophoblasts

Proprietary prenatal test (the Luna Prenatal test) analyzes a single fetal cell (trophoblast). The critical step for cell-based NIPT is the recovery of rare fetal cells (e.g., trophoblasts). For this testing, 30–40 mL of blood is collected at 10–16 weeks' gestation, followed by density fractionation or magnetic activated cell sorting (MACS) with anti-trophoblast antibodies to enrich the nucleated cells. Then, the nucleated cells are immunostained to identify trophoblasts that are cytokeratin positive and leukocyte common antigen (CD45) negative. The stained cells are picked individually under fluorescence microscopy with an automatic instrument and subjected to whole genome amplification (WGA), which allows downstream genotyping, and copy number analysis using array Comparative Genomic Hybridization (CGH) or next generation sequencing (NGS).

An overview of recent developments in cell-based noninvasive prenatal testing (2021, L. Vossaert) noted that one of the main challenges is consistent recovery of a sufficient number of cells from each patient to reduce the percent of test failures. Other aspects to consider when evaluating for clinical implementation are turn-around-time, scalability, throughput, and cost. While promising, more work is needed to increase the throughput of current protocols and guarantee consistent test performance.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Act for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of noninvasive prenatal screening tests using cell-free fetal DNA.

Commercially available tests include but are not limited to the following:

- Myriad Prequel™‡ Prenatal Screen (Myriad Women's Health, Counsyl) utilizes whole genome sequencing for detecting aneuploidy including T21, T18, T13.
- VisibiliT (Sequenom Laboratories, now LabCorp) tests for T21 and T18, and tests for sex.
- MaterniT®‡21 PLUS (Sequenom Laboratories, now LabCorp) core test includes T21, T18, T13, and fetal sex aneuploidies. The enhanced sequencing series includes testing for T16, T22, and 7 microdeletions: 22q deletion syndrome (DiGeorge syndrome), 5p (cri du chat syndrome), 15q (Prader-Willi and Angelman syndromes), 1p36 deletion syndrome, 4p (Wolf-Hirschhorn syndrome), 8q (Langer-Giedion syndrome), and 11q (Jacobsen syndrome). The test uses MPS and reports results as positive or negative. The enhanced sequencing series is offered on an opt-out basis.
- Harmony®‡ (Ariosa Diagnostics, now Roche) tests for T21, T18, and T13. The test uses directed DNA analysis and results are reported as a risk score.
- Panorama™‡ (Natera) is a prenatal test for detecting T21, T18, and T13, as well as select sex chromosome abnormalities. It uses single nucleotide variant technology; results are reported as a risk score. An extended panel tests for 5 microdeletions: 22q deletion syndrome (DiGeorge syndrome), 5p (cri du chat syndrome), 15q11-13 (Prader-Willi and Angelman syndromes), and 1p36 deletion syndrome. Screening for 22q11.2 will be included in the panel unless the opt-out option is selected; screening for the remaining 4 microdeletions is offered on an opt-in basis.
- Verifi®‡ (Verinata Health, now Illumina) is a prenatal test for T21, T18, and T13. The test uses MPS and calculates a normalized chromosomal value, reporting results as 1 of 3 categories: no aneuploidy detected, aneuploidy detected, or aneuploidy suspected.

- InformaSeq (Integrated Genetics, now LabCorp) is a prenatal test for detecting T21, T18, and T13, with optional testing for select sex chromosome abnormalities. It uses the Illumina platform and reports results in a similar manner.
- QNatal®‡ Advanced (Quest Diagnostics) tests for T21, T18, and T13.
- Vanadis NIPT Solution (PerkinElmer) tests for T21, T18, and T13.
- Veracity®‡ (NIPD Genetics) tests for T21, T18, and T13, sex chromosome aneuploidies, and microdeletions.
- Vistara™‡ Single-Gene NIPT tests 25 autosomal dominant and X-linked conditions across 30 genes.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

For individuals who have a singleton pregnancy who receive NIPS for T21, T18, and T13 using cell-free fetal DNA, the evidence includes observational studies and systematic reviews. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Published studies on available tests and meta-analyses of these studies have consistently demonstrated very high sensitivity and specificity for detecting Down syndrome (T21) in singleton pregnancies. Most studies included only individuals at high risk of T21, but several studies have reported similar levels of diagnostic accuracy in average-risk individuals. Compared with standard serum screening, both the sensitivity and specificity of cell-free fetal DNA screening are considerably higher. As a result, screening with cell-free fetal DNA for T21 will result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures. Screening for T18 and T13 along with T21 may allow for preparation for fetal demise or termination of the pregnancy prior to fetal loss. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a singleton pregnancy who receive NIPS for sex chromosome aneuploidies using cell-free fetal DNA, the evidence includes observational studies, mainly in high-risk pregnancies, and systematic reviews. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Meta-analyses of available data have suggested high sensitivities and specificities, but the small number of cases makes definitive conclusions difficult. In addition, the clinical utility of identifying sex chromosome aneuploidies during pregnancy is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a twin pregnancy who receive NIPS for aneuploidies using cell-free fetal DNA, the evidence includes observational studies and systematic reviews. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The small number of cases of aneuploidy identified in studies resulted in wide confidence intervals and estimates that are too imprecise to allow conclusions about clinical validity. There is a lack of direct evidence of clinical utility, and a chain of evidence cannot be conducted due to insufficient evidence on clinical validity. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with pregnancy(ies) who receive NIPS for microdeletions using cell-free fetal DNA, the evidence includes several observational studies. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The available studies on clinical validity have limitations (eg, missing data on confirmatory testing, false-negatives), and the added benefit of NIPS compared with current approaches is unclear. Moreover, the clinical utility of NIPS for microdeletions remains unclear and has not been evaluated in published studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have twin pregnancy who receive noninvasive prenatal testing (NIPT) for twin zygosity using cell-free fetal DNA, the evidence includes an observational study. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. Sensitivity and specificity were high (100%) in 1 validation study conducted in 95 twin gestations. This evidence is too limited to draw conclusions about performance characteristics and would need to be confirmed in additional, well-conducted studies. Moreover, the clinical utility of NIPT for twin zygosity compared to standard methods, such as ultrasound, is unclear and has not been evaluated in published studies.

The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a singleton pregnancy who receive NIPS for T21, T18, and T13 using Vanadis NIPT, the evidence includes 2 industry sponsored studies. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The available studies on clinical validity have limitations, and the added benefit of Vanadis NIPT compared with current approaches is unclear. Moreover, the clinical utility of Vanadis NIPT remains unclear and has not been evaluated in published studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with pregnancies who receive NIPS for single-gene disorders using Vistara Single-Gene NIPT, the evidence includes 1 validation study and a case series of 2208 pregnancies. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. There is no direct evidence of clinical utility and a chain of evidence cannot be conducted due to insufficient evidence on clinical validity. There is a potential that prenatal identification of pregnancies with single-gene disorders could improve health outcomes due to the ability to allow for informed reproductive decision making and/or initiate earlier treatment; however, data demonstrating improvement are unavailable. Given the variability of single-gene disorders identified by the test and the lack of experience with routine genetic screening for single-gene disorders, clinical decision making based on the Vistara NIPT is not well defined. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine
In 2020, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine released a joint practice bulletin summary (No. 226) on the screening for fetal chromosomal abnormalities.

The following recommendations related to cell-free DNA screening were based on "good and consistent" scientific evidence (Level A):

- "Prenatal genetic screening (serum screening with or without nuchal translucency ultrasound or cell-free DNA screening) and diagnostic testing (chorionic villus sampling or amniocentesis) options should be discussed and offered to all pregnant women regardless of maternal age or risk of chromosomal abnormality. After review and discussion, every patient has the right to pursue or decline prenatal genetic screening and diagnostic testing."
- "If screening is accepted, patients should have one prenatal screening approach, and should not have multiple screening tests performed simultaneously."
- "Cell-free DNA is the most sensitive and specific screening test for the common fetal aneuploidies. Nevertheless, it has the potential for false-positive and false-negative results. Furthermore, cell-free DNA testing is not equivalent to diagnostic testing."
- "Patients with a positive screening test result for fetal aneuploidy should undergo genetic counseling and a comprehensive ultrasound evaluation with an opportunity for diagnostic testing to confirm results."
- "Patients with a negative screening test result should be made aware that this substantially decreases their risk of the targeted aneuploidy but does not ensure that the fetus is unaffected. The potential for a fetus to be affected by genetic disorders that are not evaluated by the screening or diagnostic test should also be reviewed. Even if patients have a negative screening test result, they may choose diagnostic testing later in pregnancy, particularly if additional findings become evident such as fetal anomalies identified on ultrasound examination."
- "Patients whose cell-free DNA screening test results are not reported by the laboratory or are uninterpretable (a no-call test result) should be informed that test failure is associated with an increased risk of aneuploidy, receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing."

The following recommendations related to cell-free DNA screening were based on "limited or inconsistent" (Level B):

- "The use of cell-free DNA screening as follow-up for patients with a screen positive serum analyte screening test result is an option for patients who want to avoid a diagnostic test. However, patients should be informed that this approach may delay definitive diagnosis and will fail to identify some fetuses with chromosomal abnormalities."
- "In clinical situations of an isolated soft ultrasonographic marker (such as echogenic cardiac focus, choroid plexus cyst, pyelectasis, short humerus or femur length) where aneuploidy screening has not been performed, the patient should be counseled regarding the risk of aneuploidy associated with the finding and cell-free DNA, quad screen testing, or amniocentesis should be offered. If aneuploidy testing is performed and is low-risk, then no further risk assessment is needed. If more than one marker is identified, then genetic counseling, maternal–fetal medicine consultation, or both are recommended."
- "No method of aneuploidy screening that includes a serum sample is as accurate in twin gestations as it is in singleton pregnancies; this information should be incorporated into pretest counseling for patients with multiple gestations."
- "Cell-free DNA screening can be performed in twin pregnancies. Overall, performance of screening for trisomy 21 by cell-free DNA in twin pregnancies is encouraging, but the total number of reported affected cases is small. Given the small number of affected cases it is difficult to determine an accurate detection rate for trisomy 18 and 13."

The following recommendations related to cell-free DNA screening were based primarily on consensus and expert opinion (Level C):

- "The use of multiple serum screening approaches performed independently (eg, a first-trimester screening test followed by a quad screen as an unlinked test) is not recommended because it will result in an unacceptably high positive screening rate and could deliver contradictory risk estimates."
- "In multifetal gestations, if a fetal demise, vanishing twin, or anomaly is identified in one fetus, there is a significant risk of an inaccurate test result if serum-based aneuploidy screening or cell-free DNA is used. This information should be reviewed with the patient and diagnostic testing should be offered."

- "Patients with unusual or multiple aneuploidies detected by cell-free DNA should be referred for genetic counseling and maternal–fetal medicine consultation."

American College of Medical Genetics and Genomics

Noninvasive Prenatal Screening for Fetal Aneuploidies
In 2016, the American College of Medical Genetics and Genomics published a position statement on noninvasive prenatal screening (NIPS) for fetal aneuploidy. The relevant recommendations are as follows:

- "Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes)."
- "Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS."
- "Offering diagnostic testing when a positive screening test result is reported after NIPS."
- "Providing accurate, balanced, up-to-date information, at an appropriate literacy level when a fetus is diagnosed with a chromosomal or genomic variation in an effort to educate prospective parents about the condition of concern. These materials should reflect the medical and psychosocial implications of the diagnosis."

The American College of Medical Genetics and Genomics did not recommend "NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21."

Cell-free DNA Screening for Single-Gene Disorders
In a practice advisory on cell-free DNA screening for single-gene disorders published in 2019 and reaffirmed in 2021, ACOG stated, "Although this technology is available clinically and marketed as a single-gene disorder prenatal screening option for obstetric care providers to consider in their practice, often in presence of advanced paternal age, there has not been sufficient data to provide information regarding accuracy and positive and negative predictive value in the general population. For this reason, single-gene cell-free DNA screening is not currently recommended in pregnancy."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this medical policy are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03375359	First Trimester Screening for Trisomy 21, 18, 13 and 22q11.2 Deletion Syndrome - ReFaPo02	1000	Aug 2022
NCT05312814	Clinical Utility of the Addition of a SNP-based NIPT Zygosity Determination in Twin Pregnancy Management.	700	Nov 2023
NCT01545674[a]	Prenatal Non-invasive Aneuploidy Test Utilizing SNPs Trial (PreNATUS)	1000	Dec 2022
Unpublished			
NCT03559374[a]	Study of Vanadis NIPT for Non-Invasive Prenatal Screening of Trisomies (T21, T18, andT13)	1200	Aug 2020 (status unknown, last update August 2018)

NCT: national clinical trial.
[a]Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 12/20/2013
Current Effective Date: 05/01/2023

02/20/2013	Medical Policy Implementation Committee approval. New policy.
02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2015	Coding Update
02/05/2015	Medical Policy Committee review
02/18/2015	Medical Policy Implementation Committee approval. Title changed from "Sequencing-based Tests to Determine Trisomy 21 from Maternal Plasma DNA" to "Noninvasive Prenatal Testing for Fetal Aneuploidies Using Cell-Free Fetal DNA". Removed the statement from the coverage section that stated to deny as investigational if criteria are not met for clarification. Statement added that concurrent nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18 may be considered medically necessary in women who are eligible for and are undergoing nucleic acid sequencing-based testing of maternal plasma for trisomy 21. In addition, 2 investigational statements were added, 1 for nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18, other than in the situations specified in the medically necessary statement and the other for fetal sex chromosome aneuploidies.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
02/04/2016	Medical Policy Committee review
02/17/2016	Medical Policy Implementation Committee approval. Title change. Testing for microdeletions added to the policy.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes

02/02/2017	Medical Policy Committee review
02/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2017	Coding update
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Policy Guidelines section added to the policy.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Added a statement for when nucleic acid sequencing–based testing of maternal plasma for trisomy 13 and/or 18 is investigational.
09/09/2019	Coding update
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/10/2020	Coding update
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Title changed from "Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions Using Cell-Free Fetal DNA" to "Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions, and Twin Zygosity Using Cell-Free Fetal NA". Added an investigational statement for noninvasive prenatal testing for twin zygosity. Added investigational statement for noninvasive prenatal testing using Vanadis NIPT.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Revised the eligible for coverage statement to cover nucleic acid sequencing-based testing of maternal plasma to screen for trisomy 21, 18, and 13 in women with singleton pregnancies. Removed the Not Medically Necessary section. All investigational statements remain unchanged.
09/30/2021	Coding update
03/24/2022	Coding update
04/09/2022	Medical Policy Committee review

04/13/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/08/2022 Coding update
04/06/2023 Medical Policy Committee review
04/12/2023 Medical Policy Implementation Committee approval. Title changed from "Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions, and Twin Zygosity Using Cell-Free Fetal DNA" to "Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions, Single-Gene Disorders, and Twin Zygosity Using Cell-Free Fetal DNA". Replaced "women" with "individuals" in the coverage section. Replaced "singleton pregnancies" with "single or twin gestation pregnancy" as eligible for coverage with exceptions for nucleic acid sequencing-based testing of maternal plasma to screen for trisomy 21, 18, and 13. Noted which twin pregnancies are investigational and that pregnancies involving three or more fetuses are investigational. Revised the investigational statement for nucleic acid sequencing-based testing of maternal plasma in all other situations, to include more than one prenatal cell-free DNA test per pregnancy; also removed trisomy 13 and 18 from this investigational statement. Added a *Note* to the investigational section regarding separate billing/payment for chromosome and less common trisomies testing. Combined microdeletions and twin zygosity testing into one investigational statement. Added an investigational statement for Vistara NIPT of maternal plasma to screen for single-gene disorders in all situations. Removed investigational statement for nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18, other than situations specified as eligible for coverage. Added an investigational statement for single cell genotyping in trophoblasts isolated from maternal serum (e.g., Luna Prenatal Test).

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81420, 81422, 81479, 81507, 81599 Add code effective 07/01/2022: 0327U Add codes effective 05/01/2023: 0060U, 0341U, 81442, 81302
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.