BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 4.01.21 Noninvasive Prenatal Screening for Fetal Aneuploidies, Microdeletions, and Twin Zygosity Using Cell-Free Fetal DNA

Effective Policy Date: January 1, 2022

Original Policy Date: March 2013

Related Policies:

2.04.59 - Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies

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

Description

National guidelines recommend that all pregnant women be offered screening for fetal chromosomal abnormalities, most of which are aneuploidies, an abnormal number of chromosomes. Trisomy syndromes are aneuploidies involving 3 copies of 1 chromosome. Trisomies 21, 18, and 13 are the most common forms of fetal aneuploidy that survive to birth. There are numerous limitations to standard screening for these disorders using the maternal serum and fetal ultrasound. Noninvasive prenatal screening analyzing cell-free fetal DNA in maternal serum is a potential complement or alternative to conventional serum screening. Noninvasive prenatal screening (NIPS) using cell-free fetal DNA has also been proposed to screen for microdeletions. Prenatal testing for twin zygosity using cell-free fetal DNA has been proposed to inform decisions about early surveillance for twin-twin transfusion syndrome and other monochorionic twin-related abnormalities.

OBJECTIVE

The objective of this evidence review is to determine whether noninvasive testing for cell-free fetal DNA to screen for aneuploidies of chromosomes 13, 18, or 21, sex chromosome aneuploidies, or microdeletions improves the net health outcome in pregnant women compared with standard of care.

POLICY STATEMENT

Nucleic acid sequencing-based testing of maternal plasma to screen for trisomy 21, 18, and 13 may be considered **medically necessary** in women with singleton pregnancies.

Nucleic acid sequencing-based testing of maternal plasma for fetal sex chromosome aneuploidies is considered **investigational**.

Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 is considered **investigational** in women with twin or multiple pregnancies.

Nucleic acid sequencing-based testing of maternal plasma for trisomy 13 and/or 18, other than in the situations specified above, is considered **investigational**.

Nucleic acid sequencing-based testing of maternal plasma for microdeletions is considered **investigational**.

Nucleic acid sequencing-based testing of maternal plasma for twin zygosity is considered **investigational**.

Vanadis NIPT of maternal plasma to screen for trisomy 21, 18 and 13 is considered **investigational** in all situations.

POLICY GUIDELINES

Karyotyping would be necessary to exclude the possibility of a false-positive, nucleic acid sequencing-based test. Before testing, women 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 patients 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. Patients should continue to be offered ultrasound or maternal serum a-fetoprotein screening.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

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.
- MaterniT21 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.

RATIONALE

Summary of Evidence

For individuals who have a singleton pregnancy who receive noninvasive prenatal screening (NIPS) for Trisomy 21, 18 and 13 (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 women at high-risk of trisomy 21 (T21), but several studies have reported similar levels of diagnostic accuracy in average-risk women. 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 trisomy 18 (T18) and trisomy 13 (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 total number of cases of aneuploidy identified in these studies is fewer than 300, resulting 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. **T**he 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. **T**he 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.[27,]

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

In 2016, the American College of Medical Genetics and Genomics published a position statement on noninvasive prenatal screening (NIPS) for fetal aneuploidy.[28.] 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."

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force does not currently address screening for Down syndrome. This syndrome was addressed in the 1990s; it is no longer listed on the Task Force website.

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2013	New policy	
March 2014	Replace policy	Policy updated with literature review. References 12, 14, 18, 22-24 added. No change to policy statement.
September 2014	Replace policy	Policy updated with literature review adding references 13 and 14. The title was changed to Noninvasive Prenatal Testing for Trisomy 21 Using Cell Free Fetal DNA. The policy statements are unchanged.
March 2015	Replace policy	Policy updated with literature review through October 1, 2014. 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. References 4, 16, 20 and 24 added. In title, "Trisomy 21" changed to "Fetal Aneuploidies".
December 2015	Replace policy	Policy updated with literature review through August 31, 2015; references 1, 4, 20-21, 25-28, 31, and 34-35 added. "High-risk" was removed from medically necessary statement. Investigational statement on average-risk women was removed. Statement added that nucleic acid sequencing-based testing of maternal plasma for microdeletions is considered investigational. In the title, "testing" was changed to "screening" and "And Microdeletions" was added to the title.
March 2017	Replace policy	Policy updated with literature review, references 8-9, 27, 34-35, and 38 added. Policy statements unchanged.
December 2017	Replace policy	Policy updated with literature review through June 22, 2017; references 10, 25-27, and 40-41 added; note 35 replaced. Policy statements unchanged.
March 2018	Replace policy	Removed non-FEP policy which was listed under related policies: 2.04.107 Carrier Testing for Genetic Diseases and 2.04.116 Invasive Prenatal (Fetal) Diagnostic Testing.
December 2018	Replace policy	Policy updated with literature review through June 4, 2018; Rationale section revised; references 5, 7, and 12 added; some references removed. The first policy statement revised to indicate that noninvasive prenatal screening for trisomies 21, 18, and 13 maybe considered medically necessary. The second policy statement on trisomies 18 and 13 was deleted.
December 2019	Replace policy	Policy updated with literature review through Jun 26, 2019; references added. Policy statements unchanged.
December 2020	Replace policy	Policy updated with literature review through July 24, 2020; references added. Added indication and investigational statement for noninvasive prenatal testing for twin zygosity. Policy title changed to include the new indication. Added investigational statement for noninvasive prenatal testing using Vanadis NIPT.
December 2021	Replace policy	Policy updated with literature review through June 28, 2021; references added. Revised language in Indication 3 to clarify the evidence review refers to twin, not higher order multiple, gestations. Policy statements unchanged.