BlueCross BlueShield Federal Employee Program.

FEP 4.01.21 Noninvasive Prenatal Screening for Fetal Aneuploidies Using Cell-Free Fetal DNA

Effective Date: January 15, 2019

Related Policies:
2.04.59 Genetic Testing for Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and Congenital Anomalies
2.04.116 Invasive Prenatal (Fetal) Diagnostic Testing

Noninvasive Prenatal Screening for Fetal Aneuploidies 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 (T21), 18 (T18), and 13 (T13) are the most common forms of fetal aneuploidy. Fetuses with T18 and T13 generally do not survive to birth. There are numerous limitations to standard screening for these disorders using maternal serum and fetal ultrasound. Noninvasive prenatal screening (NIPS) analyzing cell-free fetal DNA in maternal serum is a potential complement or alternative to conventional serum screening. NIPS using cell-free fetal DNA has also been proposed to screen for microdeletions.

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**.

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 risk of neural tube defects. Patients should continue to be offered ultrasound or maternal serum α-fetoprotein screening.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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:

- The 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.

RATIONALE

Summary of Evidence

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 women at high risk of 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 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 a meaningful 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 the effects of the technology on health outcomes.

For individuals who have a twin or multiple pregnancy who receive NIPS for aneuploidies using cell-free fetal DNA, the evidence includes observational studies and a systematic review. Relevant outcomes are test accuracy and validity, morbid events, and resource utilization. The total number of cases of aneuploidy identified in these studies is small and is insufficient to draw conclusions about clinical validity. There is a lack of direct evidence of clinical utility, and a chain of evidence cannot be conducted due to the paucity of evidence on clinical validity. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2016) released a joint practice bulletin summary (No. 163) on the screening for fetal aneuploidy.[13] The following recommendations on cell-free DNA were based on “good and consistent” scientific evidence:

> “Women who have a negative screening test result should not be offered additional screening tests for aneuploidy because this will increase their potential for a false-positive test result.”

"Because cell-free DNA is a screening test with the potential for false-positive and false-negative results, such testing should not be used as a substitute for diagnostic testing."
"All women with a positive cell-free DNA test result should have a diagnostic procedure before any irreversible action, such as pregnancy termination, is taken."
"Women whose cell-free DNA screening test results are not reported, are indeterminate, or are uninterpretable (a no call test result) should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy."

The following recommendations were based on "limited or inconsistent" scientific evidence:

"Cell-free DNA screening tests for microdeletions have not been validated clinically and are not recommended at this time."
"No method of aneuploidy screening is as accurate in twin gestations as it is in singleton pregnancies. Because data generally are unavailable for higher-order multifetal gestations, analyte screening for fetal aneuploidy should be limited to singleton and twin pregnancies."

The following recommendations are based "primarily on consensus and expert opinion":

"Some women who receive a positive test result from traditional screening may prefer to have cell-free DNA screening rather than undergo definitive testing."
"This approach may delay definitive diagnosis and management and may fail to identify some fetuses with aneuploidy."
"Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost effective and should not be performed."

American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (2016) published a position statement on NIPS for fetal aneuploidy.[14] 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 College did not recommend "NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21."

International Society for Prenatal Diagnosis

The International Society for Prenatal Diagnosis (2015) published a position statement on the prenatal diagnosis of chromosomal abnormalities, updating its 2013 statement.[15,16] (Note that a number of the authors of the 2015 report had financial links to industry.) The following summarizes the Society's recommendations:

I. High sensitivities and specificities are potentially achievable with cfDNA [cell-free DNA] screening for some fetal aneuploidies, notably trisomy 21.
II. Definitive diagnosis of Down syndrome and other fetal chromosome abnormalities can only be achieved through testing on cells obtained by amniocentesis or CVS [chorionic villous sampling].

III. The use of maternal age alone to assess fetal Down syndrome risk in pregnant women is not recommended.
IV. A combination of ultrasound NT [nuchal translucency] measurement and maternal serum markers in the first trimester should be available to women who want an early risk assessment and for whom cfDNA screening cannot be provided.
V. A four-marker serum test should be available to women who first attend for their prenatal care after 13 weeks 6 days of pregnancy and where cfDNA screening cannot be provided.
VI. Protocols that combine first trimester and second trimester conventional markers are valid.
VII. Second trimester ultrasound can be a useful adjunct to conventional aneuploidy screening protocols.
VIII. When cfDNA screening is extended to microdeletion and microduplication syndromes or rare trisomies the testing should be limited to clinically significant disorders or well defined severe conditions. There should be defined estimates for the detection rates, false-positive rates, and information about the clinical significance of a positive test for each disorder being screened."

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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
March 2013	New Policy	
March 2014	Update Policy	Policy updated with literature review. References 12, 14, 18, 22-24 added. No change to policy statement.
September 2014	Update 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	Update 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	Update 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	Update Policy	Policy updated with literature review, references 8-9, 27, 34-35, and 38 added. Policy statements unchanged.
December 2017	Update 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	Administrative Update	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	Update 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.