BlueCross BlueShield Federal Employee Program.

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

Effective Date: April 15, 2018

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

Noninvasive Prenatal Screening for Fetal Aneuploidies and Microdeletions 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 that 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.

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:

- VisibiliT™ (Sequenom Laboratories, now LabCorp) tests for T21 and T18, and tests for sex.
- MateriT21™ PLUS (Sequenom Laboratories) core test includes T21, T18, and T13 and fetal sex aneuploidies. The enhanced sequencing series includes testing for T16 and 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 one of three categories: no aneuploidy detected, aneuploidy detected, or aneuploidy suspected.
- InformaSeq^{SM} (Integrated Genetics) is a prenatal test for detecting T21, T18, and T13, with optional additional testing for select sex chromosome abnormalities. It uses the Illumina platform and reports results in similar manner.
- QNatal Advanced™ (Quest Diagnostics) tests for T21, T18, and T13.

POLICY STATEMENT

Nucleic acid sequencing–based testing of maternal plasma for trisomy 21 may be considered **medically necessary** in women with singleton pregnancies undergoing screening for trisomy 21. (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 [see Policy Guidelines section]).

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.

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 fetal sex chromosome aneuploidies is considered **investigational**.

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

POLICY GUIDELINES

This policy does not apply to pregnancies with a high clinical suspicion of fetal microdeletions for which invasive confirmatory testing is indicated.

In a 2015 committee opinion, the American College of Obstetricians and Gynecologists (ACOG) 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. In these studies, the actual false-positive test results were not always borderline; some were clearly above the assay cutoff value, and no processing or biologic explanations for the false-positive results were reported. False-positive findings have been found to be associated with factors including placental mosaicism, vanishing twins, and maternal malignancies. In its 2015 committee opinion, ACOG recommended diagnostic testing to confirm positive cell-free fetal DNA tests, and that management decisions not be based solely on the results of cell-free fetal DNA testing. ACOG 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.

As noted in the 2015 ACOG committee opinion, cell-free fetal DNA screening does not assess risk of anomalies such as neural tube defects. Patients should continue to be offered ultrasound or maternal serum alpha-fetoprotein screening, regardless of the type of serum screening selected.

Genetics Nomenclature Update

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 Human Genome Variation Society nomenclature is recommended by the Human Genome Variation Society, the Human Variome Project, and the Human Genome Organization.

The American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, and 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

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

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. 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).

RATIONALE

Summary of Evidence

For individuals who have a singleton pregnancy who receive NIPS for T21 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 commercially 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, including one with a large sample size, 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 will result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures. 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 T18, T13, or 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, especially for T13, makes definitive conclusions difficult. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have twin or multiple pregnancies who receive NIPS for aneuploidies using cell-free fetal DNA, the evidence includes several 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 insufficient 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

In 2015, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) updated its joint committee opinion on noninvasive testing for fetal aneuploidy (No. 640).[32] The complete list of recommendations in the 2015 committee opinion follows:

- "A discussion of the risks, benefits, and alternatives of various methods of prenatal screening and diagnostic testing, including the option of no testing, should occur with all patients.
- Given the performance of conventional screening methods, the limitations of cell-free DNA screening performance, and the limited data on cost-effectiveness in the low-risk obstetric

population, conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population.

- Although any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of her risk status, the patient choosing this testing should understand the limitations and benefits of this screening paradigm in the context of alternative screening and diagnostic options.
- The cell-free DNA test will screen for only the common trisomies and, if requested, sex chromosome composition.
- Given the potential for inaccurate results and to understand the type of trisomy for recurrence-risk counseling, a diagnostic test should be recommended for a patient who has a positive cell-free DNA test result.
- Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost-effective and should not be performed.
- Management decisions, including termination of the pregnancy, should not be based on the results of the cell-free DNA screening alone.
- Women whose results are not reported, indeterminate, or uninterpretable (a 'no call' test result) from cell-free DNA screening should receive further genetic counseling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy.
- Routine cell-free DNA screening for microdeletion syndromes should not be performed.
- Cell-free DNA screening is not recommended for women with multiple gestations.
- If a fetal structural anomaly is identified on ultrasound examination, diagnostic testing should be offered rather than cell-free DNA screening.
- Patients should be counseled that a negative cell-free DNA test result does not ensure an unaffected pregnancy.
- Cell-free DNA screening does not assess risk of fetal anomalies such as neural tube defects or ventral wall defects; patients who are undergoing cell-free DNA screening should be offered maternal serum alpha-fetoprotein screening or ultrasound evaluation for risk assessment.
- Patients may decline all screening or diagnostic testing for aneuploidy."

Late in 2015, SMFM published a special report clarifying its recommendations on cell-free DNA screening, as follows[33]:

> "The purpose of this statement is to clarify that SMFM does not recommend that cfDNA [cell-free DNA] aneuploidy screening be offered to all pregnant women, nor does it suggest a requirement for insurance coverage for cfDNA screening in women at low risk of aneuploidy. However, SMFM believes, due to the ethics of patient autonomy, that the option should be available to women who request additional testing beyond what is currently recommended by professional societies.… SMFM recognizes the value of cfDNA screening for women at higher risk for aneuploidy but considers that cfDNA screening is not the appropriate choice for first-line screening for the low-risk obstetric population at the present time. For this population, conventional screening methods remain the preferred approach...."

In 2016, ACOG and SMFM released a joint practice bulletin summary (No. 163) on screening for fetal aneuploidy.[34] The following recommendations cell-free DNA are 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 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."

European Society of Human Genetics and American Society of Human Genetics

In 2015, the European Society of Human Genetics and the American Society of Human Genetics issued a joint statement on noninvasive prenatal screening (NIPS; also called noninvasive prenatal testing [NIPT]).[35] Relevant recommendations are as follows:

1. "NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFTS [combined first-trimester screening]. However, a positive NIPT result should not be regarded as a final diagnosis: false positives occur for a variety of reasons (including that the DNA sequenced is both maternal and fetal in origin, and that the fetal fraction derives from the placenta as well as the developing fetus). Thus women should be advised to have a positive result confirmed through diagnostic testing, preferably by amniocentesis, if they are considering a possible termination of pregnancy.
2. The better test performance, including lower invasive testing rate of NIPT-based screening should not lead to lower standards for pretest information and counseling. This is especially important in the light of the aim of providing pregnant women with meaningful options for reproductive choice. There should be specific attention paid to the information needs of women from other linguistic and cultural backgrounds or who are less health literate.
3. If NIPT is offered for a specific set of conditions (eg trisomies 21, 18 and 13), it may not be reasonably possible to avoid additional findings, such as other chromosomal anomalies or large scale insertions or deletions. As part of pretest information, women and couples should be made aware of the possibility of such additional findings and the range of their implications. There should be a clear policy for dealing with such findings, as much as possible also taking account of pregnant women's wishes with regard to receiving or not receiving specific information.
4. Expanding NIPT-based prenatal screening to also report on sex chromosomal abnormalities and microdeletions not only raises ethical concerns related to information and counseling challenges

but also risks reversing the important reduction in invasive testing achieved with implementation of NIPT for aneuploidy, and is therefore currently not recommended."

National Society of Genetic Counselors

In 2013, the National Society of Genetic Counselors published a position statement on NIPS of cell-free DNA in maternal plasma.[36] The Society supported noninvasive cell-free DNA testing as an option in women who want testing for aneuploidy. The document indicated that the test has been primarily validated in pregnancies considered to be at increased risk of aneuploidy, and the organization does not support routine first-tier screening in low-risk populations. Additionally, the document stated that test results should not be considered diagnostic, and abnormal findings should be confirmed through conventional diagnostic procedures, such as chronic villous sampling and amniocentesis.

American College of Medical Genetics and Genomics

In 2016, the American College of Medical Genetics and Genomics (ACMG) published a position statement on NIPS for fetal aneuploidy.[37] Relevant ACMG 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."

ACMG did not recommend "NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21."

International Society for Prenatal Diagnosis

In 2015, the International Society for Prenatal Diagnosis published a position statement on the prenatal diagnosis of chromosomal abnormalities, updating its 2013 statement.[38,39] (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

Not applicable.

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.

REFERENCES

1. Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. JAMA. Apr 15 1983;249(15):2034-2038. PMID 6220164
2. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. Obstet Gynecol. Jan 2007;109(1):217-227. PMID 17197615
3. McDonald-McGinn DM, Emanuel BE, Zacka EH. 22q11.2 Deletion Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2013.
4. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Sequencing-based tests to determine fetal down syndrome (trisomy 21) from maternal plasma DNA. TEC Assessment Program. 2013;Volume 27:Tab 10. PMID
5. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Noninvasive prenatal cell-free fetal DNA-based screening for aneuploides other than trisomy 21. TEC Assessment Program. 2014;Volume 29:Tab 7. PMID
6. Food and Drug Adminstration (FDA). Ultra High Throughput Sequencing for Clinical Diagnostic Applications - Approaches to Assess Analytical Validity, June 23, 2011 (Archived Content). https://www.federalregister.gov/documents/2011/05/19/2011-12310/ultra-high-throughput-sequencing-for-clinical-diagnostic-applications-approaches-to-assess. Accessed June 27, 2017.
7. Mackie FL, Hemming K, Allen S, et al. The accuracy of cell-free fetal DNA-based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis. BJOG. Jan 2017;124(1):32-46. PMID 27245374
8. Taylor-Phillips S, Freeman K, Geppert J, et al. Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis. BMJ Open. Jan 18 2016;6(1):e010002. PMID 26781507
9. Gil MM, Akolekar R, Quezada MS, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: meta-analysis. Fetal Diagn Ther. Feb 8 2014;35(3):156-173. PMID 24513694
10. Iwarsson E, Jacobsson B, Dagerhamn J, et al. Analysis of cell-free fetal DNA in maternal blood for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population - a systematic review and meta-analysis. Acta Obstet Gynecol Scand. Jan 2017;96(1):7-18. PMID 27779757
11. Palomaki GE, Deciu C, Kloza EM, et al. DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study. Genet Med. Mar 2012;14(3):296-305. PMID 22281937
12. Palomaki GE, Kloza EM, Lambert-Messerlian GM, et al. DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. Genet Med. Nov 2011;13(11):913-920. PMID 22005709
13. Ehrich M, Deciu C, Zwiefelhofer T, et al. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. Am J Obstet Gynecol. Mar 2011;204(3):205 e201-211. PMID 21310373
14. Bianchi DW, Platt LD, Goldberg JD, et al. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. Obstet Gynecol. May 2012;119(5):890-901. PMID 22362253
15. Sehnert AJ, Rhees B, Comstock D, et al. Optimal detection of fetal chromosomal abnormalities by massively parallel DNA sequencing of cell-free fetal DNA from maternal blood. Clin Chem. Jul 2011;57(7):1042-1049. PMID 21519036

16. Norton ME, Brar H, Weiss J, et al. Non-Invasive Chromosomal Evaluation (NICE) Study: results of a multicenter prospective cohort study for detection of fetal trisomy 21 and trisomy 18. Am J Obstet Gynecol. Aug 2012;207(2):137 e131-138. PMID 22742782
17. Ashoor G, Syngelaki A, Wagner M, et al. Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18. Am J Obstet Gynecol. Apr 2012;206(4):322 e321-325. PMID 22464073
18. Sparks AB, Struble CA, Wang ET, et al. Noninvasive prenatal detection and selective analysis of cell-free DNA obtained from maternal blood: evaluation for trisomy 21 and trisomy 18. Am J Obstet Gynecol. Apr 2012;206(4):319 e311-319. PMID 22464072
19. Nicolaides KH, Syngelaki A, Gil M, et al. Validation of targeted sequencing of single-nucleotide polymorphisms for non-invasive prenatal detection of aneuploidy of chromosomes 13, 18, 21, X, and Y. Prenat Diagn. Jun 2013;33(6):575-579. PMID 23613152
20. Porreco RP, Garite TJ, Maurel K, et al. Noninvasive prenatal screening for fetal trisomies 21, 18, 13 and the common sex chromosome aneuploidies from maternal blood using massively parallel genomic sequencing of DNA. Am J Obstet Gynecol. Oct 2014;211(4):365 e361-312. PMID 24657131
21. Norton ME, Baer RJ, Wapner RJ, et al. Cell-free DNA vs sequential screening for the detection of fetal chromosomal abnormalities. Am J Obstet Gynecol. Jun 2016;214(6):727 e721-726. PMID 26709085
22. Zhang H, Gao Y, Jiang F, et al. Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146,958 pregnancies. Ultrasound Obstet Gynecol. May 2015;45(5):530-538. PMID 25598039
23. Garfield SS, Armstrong SO. Clinical and cost consequences of incorporating a novel non-invasive prenatal test into the diagnostic pathway for fetal trisomies. J Managed Care Med. 2012;15(2):34-41. PMID
24. Ohno M, Caughey A. The role of noninvasive prenatal testing as a diagnostic versus a screening tool--a cost-effectiveness analysis. Prenat Diagn. Jul 2013;33(7):630-635. PMID 23674316
25. Gil MM, Accurti V, Santacruz B, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. Apr 11 2017. PMID 28397325
26. Du E, Feng C, Cao Y, et al. Massively parallel sequencing (MPS) of cell-free fetal DNA (cffDNA) for trisomies 21, 18, and 13 in twin pregnancies. Twin Res Hum Genet. Jun 2017;20(3):242-249. PMID 28485265
27. Fosler L, Winters P, Jones KW, et al. Aneuploidy screening by non-invasive prenatal testing in twin pregnancy. Ultrasound Obstet Gynecol. Apr 2017;49(4):470-477. PMID 27194226
28. Wapner RJ, Babiarz JE, Levy B, et al. Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes. Am J Obstet Gynecol. Mar 2015;212(3):332 e331-339. PMID 25479548
29. Gross SJ, Stosic M, McDonald-McGinn DM, et al. Clinical experience with single-nucleotide polymorphism-based non-invasive prenatal screening for 22q11.2 deletion syndrome. Ultrasound Obstet Gynecol. Feb 2016;47(2):177-183. PMID 26396068
30. Helgeson J, Wardrop J, Boomer T, et al. Clinical outcome of subchromosomal events detected by whole-genome noninvasive prenatal testing. Prenat Diagn. Oct 2015;35(10):999-1004. PMID 26088833
31. Zhao C, Tynan J, Ehrich M, et al. Detection of fetal subchromosomal abnormalities by sequencing circulating cell-free DNA from maternal plasma. Clin Chem. Apr 2015;61(4):608-616. PMID 25710461
32. Committee Opinion No. 640: Cell-free DNA Screening for Fetal Aneuploidy. Obstet Gynecol. Jun 29 2015. PMID 26114726
33. Society for Maternal-Fetal Medicine Publications Committee. Electronic address eso. SMFM Statement: clarification of recommendations regarding cell-free DNA aneuploidy screening. Am J Obstet Gynecol. Dec 2015;213(6):753-754. PMID 26458766
34. Practice Bulletin No. 163 Summary: Screening for Fetal Aneuploidy. Obstet Gynecol. May 2016;127(5):979-981. PMID 27101120
35. Dondorp W, de Wert G, Bombard Y, et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Eur J Hum Genet. Oct 2015;23(11):1438-1450. PMID 25782669
36. Devers PL, Cronister A, Ormond KE, et al. Noninvasive prenatal testing/noninvasive prenatal diagnosis: the position of the National Society of Genetic Counselors. J Genet Couns. Jun 2013;22(3):291-295. PMID 23334531
37. Gregg AR, Skotko BG, Benkendorf JL, et al. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. Oct 2016;18(10):1056-1065. PMID 27467454

38. Benn P, Borrell A, Chiu RW, et al. Position statement from the Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. Prenat Diagn. Aug 2015;35(8):725-734. PMID 25970088
39. Benn P, Borell A, Chiu R, et al. Position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis. Prenat Diagn. Jul 2013;33(7):622-629. PMID 23616385
40. Nicolaides KH, Syngelaki A, Ashoor G, et al. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. Am J Obstet Gynecol. Nov 2012;207(5):374 e371-376. PMID 23107079
41. Pergament E, Cuckle H, Zimmermann B, et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. Obstet Gynecol. Aug 2014;124(2 Pt 1):210-218. PMID 25004354

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.