BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.108 Noninvasive Fetal RHD Genotyping Using Cell-Free Fetal DNA

Annual Effective Policy Date: January 1, 2026

Original Policy Date: March 2014

Related Policies:

None

Noninvasive Fetal RHD Genotyping Using Cell-Free Fetal DNA

Description

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Rhesus D (RhD)-negative women who are exposed to RhD-positive red blood cells can develop anti-RhD antibodies, which can cross the placenta and cause fetal anemia. If undiagnosed and untreated, alloimmunization can cause significant perinatal morbidity and mortality. Determining the RhD status of the fetus may guide subsequent management of the pregnancy. Hence, the use of cell-free fetal DNA (cffDNA) in maternal blood has been proposed as a noninvasive method to determine fetal *RHD* genotype.

OBJECTIVE

The objective of this evidence review is to evaluate whether noninvasive fetal *RHD* genotyping using cell-free fetal DNA improves the net health outcome in individuals who are pregnant and have Rhesus D-negative blood type.

POLICY STATEMENT

Measurement of cell-free DNA for fetal genotyping for RhD antigen may be **medically necessary** when all of the following criteria are met:

1. Pregnancy may be at risk for alloimmunization due to maternal RhD negative status or the presence of maternal red cell antigen antibodies; and
2. Paternal antigen typing is unavailable or heterozygous; and
3. Amniocentesis is declined or contraindicated.

POLICY GUIDELINES

Genetics Nomenclature Update

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

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. American College of Medical Genetics and Genomics-Association for Molecular Pathology 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

BENEFIT APPLICATION

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

Some plans may have contract or benefit exclusions for genetic testing.

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 Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

The proprietary SensiGene™ Fetal RHD Genotyping test SEQureDx™ technology was marketed by Sequenom. The assay targets exons 4, 5, and 7 of the *RHD* gene located on chromosome 1, psi (ψ) pseudogene in exon 4, and assay controls, which are 3 targets on the Y chromosome (SRY, TTTY, DBY) using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry-based nucleic acid analysis. The company claims that uses of its test include:

- Clarifying fetal RhD status without testing the father, thereby avoiding the cost of paternity testing and paternal genotyping.
- Clarifying fetal RhD status when maternal anti-D titers are unclear.
- Identifying the RhD-negative fetus in mothers who are opposed to immunization(s) and vaccines.
- Identifying RhD-negative sensitized patients.
- Avoiding invasive testing by CVS or genetic amniocentesis.

At the time of the 2025 policy update, the availability of the SensiGene™ Fetal RHD Genotyping test could not be confirmed. The evidence review no longer considers this test.

Another noninvasive RhD test is the Unity Screen™ test from BillionToOne. In addition to testing for RhD, the test evaluates the C, c, D, E, Fy^a, and K antigens, aneuploidy, and recessive conditions including cystic fibrosis, spinal muscular atrophy, sickle cell disease, alpha and beta thalassemia, and fragile X syndrome. The Unity Screen test uses a proprietary technology (Quantitative Counting Templates) to quantify fetal DNA with as little as a single base pair alteration. The quantitative counting templates are traceable synthetic DNA fragments that are added to the patient's sample. After amplification, the number of fragments is added to a calculation that determines the number of DNA fragments of interest in the patient sample.

Natera offers an add-on fetal RhD test to its noninvasive prenatal Panorama™ test, which uses next-generation sequencing technology. The manufacturer states that Panorama is the only single nucleotide polymorphism-based noninvasive prenatal test. More than 13,000 single nucleotide polymorphisms are included in the screening test. The assay involves DNA primers to regions that specifically identify the RHD psi (ψ) pseudogene.

RATIONALE

Summary of Evidence

For individuals who are pregnant and have Rhesus D (RhD)-negative blood type who receive noninvasive *RHD* genotyping of the fetus using cell-free DNA from maternal plasma, the evidence for clinical validity includes 2 meta-analyses and additional prospective studies and one retrospective cohort for clinical utility. Relevant outcomes are test validity, morbid events, medication use, and treatment-related morbidity. Clinical validity studies have demonstrated that the sensitivity of both currently available tests are 100% and the specificity of both tests is very high (99.3% to 100%).. Prospective studies comparing outcomes in patients managed with and without the test are lacking. The American College of Obstetricians and Gynecologists endorses cell-free fetal DNA testing in pregnancies with when paternity status is unknown or heterozygous and in clinical circumstances when an alternative to amniocentesis is recommended or desired.The evidence is sufficient 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

In 2018, the American College of Obstetricians and Gynecologists reaffirmed its 2006 position that detection of fetal Rhesus D (RhD) using molecular analysis of maternal plasma or serum can be assessed in the second trimester with an accuracy greater than 99% but that this test is not a widely used clinical tool.[13,14,] This statement was last reaffirmed in 2024.

In its 2017 Practice Bulletin Number 181 on the prevention of RhD alloimmunization, the College stated that "Despite the improved accuracies noted with noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D immunoglobulin at 28 weeks of gestation have not shown a consistent benefit and, thus, this test is not routinely recommended."[15,] This statement was last reaffirmed in 2024.

Sperling et al (2018) compared the guidelines from the American College of Obstetricians and Gynecologists as well as 3 international guidelines on the prevention of RhD alloimmunization.[16,] All 4 guidelines recommended that all women have an antibody screen with an indirect Coombs test at prenatal intake and at 24 to 28 weeks. None currently recommend screening with cell-free fetal DNA.

In 2024, ACOG published updated guidance for management of alloimmunization in pregnancy.[17,] The update recommends fetal RhD antigen testing when the paternal genotype is heterozygous or unknown. Cell-free fetal DNA is described as an "alternative tool" for patients who are unwilling to undergo amniocentesis.

A 2024 Practice Advisory statement on RhD immune globulin shortages endorses using noninvasive prenatal testing with cell-free fetal DNA in the setting of a shortage to help with supply conservation efforts.[18,] Postpartum administration should be prioritized first, followed by 28 weeks of antepartum prophylaxis if there is sufficient supply.

U.S. Preventive Services Task Force Recommendations

No **U.S. Preventive Services Task Force** recommendations addressing fetal *RHD* genotyping were identified.

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.

REFERENCES

1. Daniels G, Finning K, Martin P, et al. Fetal RhD genotyping: a more efficient use of anti-D immunoglobulin. Transfus Clin Biol. Dec 2007; 14(6): 568-71. PMID 18436463
2. Moise K. Overview of Rhesus (Rh) alloimmunization in pregnancy. In: Lockwood CJ, ed. UpToDate. Waltham, MA: UpToDate; 2013.
3. Moise KJ, Argoti PS. Management and prevention of red cell alloimmunization in pregnancy: a systematic review. Obstet Gynecol. Nov 2012; 120(5): 1132-9. PMID 23090532
4. Van den Veyver IB, Moise KJ. Fetal RhD typing by polymerase chain reaction in pregnancies complicated by rhesus alloimmunization. Obstet Gynecol. Dec 1996; 88(6): 1061-7. PMID 8942854
5. Lo YM, Tein MS, Lau TK, et al. Quantitative analysis of fetal DNA in maternal plasma and serum: implications for noninvasive prenatal diagnosis. Am J Hum Genet. Apr 1998; 62(4): 768-75. PMID 9529358
6. Mustafa HJ, Najjariasl P, Aghajani F, et al. Diagnostic accuracy of cell-free DNA for the determination of fetal red blood cell antigen genotype: a systematic review and meta-analysis. Am J Obstet Gynecol. May 15 2025. PMID 40381796
7. Zhu YJ, Zheng YR, Li L, et al. Diagnostic accuracy of non-invasive fetal RhD genotyping using cell-free fetal DNA: a meta analysis. J Matern Fetal Neonatal Med. Dec 2014; 27(18): 1839-44. PMID 24422551

8. Chitty LS, Finning K, Wade A, et al. Diagnostic accuracy of routine antenatal determination of fetal RHD status across gestation: population based cohort study. BMJ. Sep 04 2014; 349: g5243. PMID 25190055
9. Alford B, Landry BP, Hou S, et al. Validation of a non-invasive prenatal test for fetal RhD, C, c, E, K and Fy a antigens. Sci Rep. Aug 07 2023; 13(1): 12786. PMID 37550335
10. Rego S, Ashimi Balogun O, Emanuel K, et al. Cell-Free DNA Analysis for the Determination of Fetal Red Blood Cell Antigen Genotype in Individuals With Alloimmunized Pregnancies. Obstet Gynecol. Oct 01 2024; 144(4): 436-443. PMID 39053010
11. Gilstrop Thompson M, Xu W, Moore B, et al. Clinical Validation of a Prenatal Cell-Free DNA Screening Test for Fetal RHD in a Large U.S. Cohort. Obstet Gynecol. Feb 01 2025; 145(2): 211-216. PMID 39591628
12. Mateus-Nino JF, Wynn J, Wiggins-Smith J, et al. Clinical Performance of Cell-Free DNA for Fetal RhD Detection in RhD-Negative Pregnant Individuals in the United States. Obstet Gynecol. Apr 01 2025; 145(4): 402-408. PMID 40014864
13. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 75: Management of alloimmunization during pregnancy. Obstet Gynecol. Aug 2006; 108(2): 457-64. PMID 16880320
14. ACOG Practice Bulletin No. 192 Summary: Management of Alloimmunization During Pregnancy. Obstet Gynecol. Mar 2018; 131(3): 611-612. PMID 29470338
15. Practice Bulletin No. 181: Prevention of Rh D Alloimmunization. Obstet Gynecol. Aug 2017; 130(2): e57-e70. PMID 28742673
16. Sperling JD, Dahlke JD, Sutton D, et al. Prevention of RhD Alloimmunization: A Comparison of Four National Guidelines. Am J Perinatol. Jan 2018; 35(2): 110-119. PMID 28910850
17. Miller RS, Mercer L, Shaffer BL, Shields AD, Gandhi M. ACOG Clinical Practice Update: Paternal and Fetal Genotyping in the Management of Alloimmunization in Pregnancy. Obstet Gynecol. 2024;144(2):e47-e49.
18. American College of Obstetricians and Gynecologists. Practice Advisory: Rho(D) Immune Globulin Shortages. July 2024. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2024/03/rhod-immune-globulin-shortages. Accessed July 2, 2025.

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

Date	Action	Description
March 2014	New policy	Fetal RHD genotyping using maternal plasma is considered investigational.
March 2015	Replace policy	Policy updated with literature review. Policy statement unchanged References 6 and 7 added.
September 2018	Replace policy	Policy updated with literature review through March 5, 2018; Policy title changed to "Noninvasive Fetal RHD Genotyping Using Cell-Free Fetal DNA.,; references 9, 11-13 added. Policy statement unchanged.
December 2019	Replace policy	Policy updated with literature review through June 10, 2019; no references added. Policy statement unchanged.
December 2020	Replace policy	Policy updated with literature review through May 22, 2020; no references added. Policy statement unchanged.
December 2021	Replace policy	Policy updated with literature review through June 20, 2021; no references added. Policy statement unchanged.
December 2022	Replace policy	Policy updated with literature review through May 16, 2022; no references added. Policy statement unchanged.
December 2023	Replace policy	Policy updated with literature review through June 18, 2023; no references added. Policy statement unchanged.
December 2024	Replace policy	Policy updated with literature review through July 1, 2024; references added. Policy statement unchanged.
December 2025	Replace policy	Policy updated with literature review through July 1, 2025; references added. Policy statement changed to medically necessary when criteria are met.