



FEP Medical Policy Manual

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

Annual Effective Policy Date: January 1, 2024

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

Noninvasive fetal *RHD* genotyping using cell-free fetal DNA is considered **investigational**.

POLICY GUIDELINES

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

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

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.

Sequenom offers the SensiGene™ Fetal RHD Genotyping test, performed by proprietary SEQuireDx™ technology. 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.

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 includes a meta-analysis and additional prospective studies (for clinical validity) and no direct evidence for clinical utility. Relevant outcomes are test validity, morbid events, medication use, and treatment-related morbidity. Clinical validity studies have demonstrated that the sensitivity and specificity of the test are high; however, the false-negative test rate, while low, is not zero, potentially leading to alloimmunization of the RhD-negative mothers in these cases. It is uncertain whether *RHD* genotyping using cell-free fetal DNA (cffDNA) will lead to improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

American College of Obstetricians and Gynecologists

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.^{10,11,}

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."^{12,}

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.¹³ 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.

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

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11. ACOG Practice Bulletin No. 192 Summary: Management of Alloimmunization During Pregnancy. *Obstet Gynecol.* Mar 2018; 131(3): 611-612. PMID 29470338
12. Practice Bulletin No. 181: Prevention of Rh D Alloimmunization. *Obstet Gynecol.* Aug 2017; 130(2): e57-e70. PMID 28742673
13. 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

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.

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