

Prenatal Cell-free DNA Testing for Fetal RhD Genotyping

- I. [Prenatal cell-free DNA testing](#) for fetal RhD genotyping is considered **medically necessary** when:
 - A. The member is pregnant, **AND**
 - B. The member is confirmed to be RhD negative, **AND**
 - C. The member is not planning to undergo amniocentesis, **AND**
 - D. One of the following:
 1. The member's practice setting is experiencing [Rho\(D\) immune globulin \(RhIG\)](#) shortages, **OR**
 2. There is documentation of an unknown or heterozygous RhD genotype in the biological father of the fetus.
- II. [Prenatal cell-free DNA testing](#) for fetal RhD genotyping is considered **investigational** for all other indications.

RATIONALE AND REFERENCES

Prenatal Cell-free DNA Testing for Fetal Blood Group Genotyping

Prenatal Cell-free DNA Testing for Fetal RhD Genotyping

American College of Obstetrics and Gynecology (ACOG)

ACOG issued a practice advisory in March 2024 due to an FDA announcement regarding a shortage of Rho(D) immune globulin (Rhlg). The advisory acknowledges that ACOG guidelines currently do not recommend routine use of prenatal cell-free DNA testing for Rh(D) status due to "cost-effectiveness analyses." However, the committee states that the use of cfDNA testing "is a reasonable consideration" in a practice that is experiencing shortages, and that if a cfDNA test confirms an Rh(D)-negative fetus, they do not recommend further Rhlg treatments.

Rho(D) Immune Globulin Shortages. Practice Advisory from The American College of Obstetricians and Gynecologists.
<https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2024/03/rhod-immune-globulin-shortages>. Published March 2024, Updated July 9th, 2024.

Additionally, ACOG issued a clinical practice update in August 2024 providing new recommendations for noninvasive cfDNA in alloimmunized patients for fetal RhD genotyping. Their updated clinical recommendation includes fetal antigen genotyping in the setting of heterozygous or unknown paternal Rh(D) genotype. They recommend consideration of fetal cell-free RhD testing as an alternative test in alloimmunized individuals who have declined invasive diagnostic procedures (p. e.1 and e.2).

Paternal and Fetal Genotyping in the Management of Alloimmunization in Pregnancy. Clinical Practice Update from The American College of Obstetricians and Gynecologists (ACOG).
https://journals.lww.com/greenjournal/abstract/2024/08000/acog_clinical_practice_update_paternal_and_fetal.34.aspx. Published August 2024.

Rego, et al.

A 2024 prospective, multisite, blinded study titled “Cell-Free DNA Analysis for the Determination of Fetal Red Blood Cell Antigen Genotype in Individuals With Alloimmunized Pregnancies” demonstrated that cfDNA testing for fetal antigen genotype, including Rh(D), was highly sensitive and specific as early as 10 weeks gestation (p. 437). Per the discussion, “Concordance between fetal antigen genotype as determined by cell-free DNA analysis and neonatal antigen genotype as determined by an outside laboratory was 100% for all 190 calls on antigens to which the pregnant person was alloimmunized. Concordance was also 100% when the antigen calls were expanded to include all 465 antigens for which the pregnant person was genotype negative, resulting in a calculated assay sensitivity and specificity of 100%” (p. 439).

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.* 2024;144(4):436-443. doi:10.1097/AOG.0000000000005692

DEFINITIONS

1. **Prenatal cell-free DNA Testing** is a screening test that is used to determine the risk of specific genetic disorders by analyzing traces of cell-free DNA (cfDNA) in a pregnant woman's blood.
2. **Singleton pregnancy** is a pregnancy with one fetus.
3. **Twin zygosity** testing is used to predict the degree of genetic similarity within each pair (i.e., monozygotic versus dizygotic). Monozygotic (genetically identical twins) are at a higher risk for pregnancy complications, such as twin-twin transfusion syndrome (TTTS).
4. **Rho(D) immune globulin (RhIG)** is a medication that is used to help manage and treat Rh-negative pregnancies