MEDICAL POLICY – 12.04.108
Noninvasive Fetal RHD Genotyping Using Cell-Free Fetal DNA

BCBSA Ref. Policy: 2.04.108
Effective Date: Aug. 1, 2018
Last Revised: July 25, 2018
Replaces: 2.04.108

RELATED MEDICAL POLICIES:
None

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

The Rhesus (Rh) factor is a protein on some people’s red blood cells. If a blood test shows the protein is on the red blood cells, the person is Rh positive. If the protein is not on the surface of the red cells, the person is Rh negative. During a pregnancy, if the mother is Rh negative but the fetus is Rh positive, during pregnancy, labor, or birth some of their blood can mix. The mother’s body then makes antibodies against the Rh protein. (An antibody is a protein made by the immune system when it detects foreign substances.) If the mother becomes pregnant again with another Rh-positive fetus, the mom’s antibodies can cross the placenta and attack the fetus’ red cells and can cause serious problems for the baby. Medication known as Rh immune globulin keeps the mother from developing antibodies to the baby’s Rh factor. This medication may be given during pregnancy or after delivery. A standard blood test is used to find out if mother and baby have compatible Rh factors. A genetic test has been developed to find out this same information. This genetic test is unproven. There is not enough medical evidence to show if this test is as good as or better than a standard blood test in determining the Rh factor.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
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<tr>
<td>Fetal RHD genotyping</td>
<td>Noninvasive fetal RHD genotyping using cell-free fetal DNA, including but not limited to the SensiGene™ Fetal RhD Genotyping test, is considered investigational.</td>
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Coding

<table>
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<th>Description</th>
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<td>CPT</td>
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<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
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</table>

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Related Information

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 1). 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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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.
Evidence Review

Description

Rhesus D (RhD)-negative women who are exposed to RhD-positive red blood cells can develop anti-Rh 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 in maternal blood has been proposed as a noninvasive method to determine fetal RHD genotype.

Background

Alloimmunization

Alloimmunization refers to the development of antibodies in a patient whose blood type is Rhesus D (RhD)-negative and who is exposed to RhD-positive red blood cells (RBCs). This most commonly occurs from fetal-placental hemorrhage and entry of fetal blood cells into maternal circulation. The management of an RhD-negative pregnant patient who is not alloimmunized and is carrying a known RhD-positive fetus, or if fetal RhD status is unknown, involves administration of RhD immunoglobulin at standardized times during the pregnancy to prevent formation of anti-RhD antibodies. If the patient is already alloimmunized, monitoring the levels of anti-RhD antibody titers and for the development of fetal anemia is performed. Noninvasive and invasive tests to determine fetal RhD status exist.

Rh Blood Groups

The Rh (Rhesus) system includes more than 100 antigen varieties found on RBCs. RhD is the most common and the most immunogenic. When people have the RhD antigen on their RBCs, they are considered to be RhD-positive; if their RBCs lack the antigen, they are considered to be RhD-negative. The RhD antigen is inherited in an autosomally dominant fashion, and a person may be heterozygous (Dd; ≈60% of Rh-positive people) or homozygous (DD; ≈40% of Rh-positive people). Homozygotes always pass the RhD antigen to their offspring, whereas
heterozygotes have a 50% chance of passing the antigen to their offspring. A person who is RhD-negative does not have the Rh antigen. Although nomenclature refers to RhD-negative as dd, there is no small d antigen (ie, they lack the RHD gene and the corresponding RhD antigen).

RhD-negative status varies among ethnic groups and is 15% in whites, 5% to 8% in blacks, and 1% to 2% in Asians and Native Americans.

In the white population, almost all RhD-negative individuals are homozygous for a deletion of the RHD gene. However, in the black population, only 18% of RhD-negative individuals are homozygous for an RHD deletion, and 66% of RhD-negative blacks have an inactive RHD pseudogene (RHDψ).¹ There are also numerous rare variants of the D antigen, which are recognized by weakness of expression of D and/or by absence of some of the epitopes of D. Some individuals with variant D antigens, if exposed to RhD-positive RBCs, can make antibodies to one or more epitopes of the D antigen.¹

RhD-negative women can have a fetus that is RhD-positive if the fetus inherits the RhD-positive antigen from the paternal father.

**Causes of Alloimmunization**

By 30 days of gestation, the RhD antigen is expressed on the RBC membrane, and alloimmunization can be caused when fetal RhD-positive RBCs enter maternal circulation and the RhD-negative mother develops anti-D antibodies.² Once anti-D antibodies are present in a pregnant woman’s circulation, they can cross the placenta and cause destruction of fetal RBCs.

The production of anti-D antibodies in RhD-negative women is highly variable and significantly affected by several factors, including the volume of fetomaternal hemorrhage, the degree of maternal immune response, concurrent ABO incompatibility, and fetal homozygosity versus heterozygosity for the D antigen. Therefore, although about 10% of pregnancies are Rh-incompatible, less than 20% of RhD-incompatible pregnancies actually lead to maternal alloimmunization.

Small fetomaternal hemorrhages of RhD-positive fetal RBCs into the circulation of an RhD-negative woman occurs in nearly all pregnancies, and percentages of fetomaternal hemorrhage increase as the pregnancy progresses: 7% in the first trimester, 16% in the second trimester, and 29% in the third trimester, with the greatest risk of RhD alloimmunization occurring at birth (15%-50%). Transplacental hemorrhage accounts for almost all cases of maternal RhD alloimmunization.
Fetomaternal hemorrhage can also be associated with miscarriage, pregnancy termination, ectopic pregnancy, invasive in-utero procedures (eg, amniocentesis), intrauterine fetal death, maternal abdominal trauma, antepartum maternal hemorrhage, and external cephalic version. Other causes of alloimmunization include inadvertent transfusion of RhD-positive blood and RhD-mismatched allogeneic hematopoietic stem cell transplantation.

**Consequences of Alloimmunization**

Immunoglobulin (Ig) G antibody–mediated hemolysis of fetal RBCs, known as hemolytic disease of the fetus and newborn, varies in severity and can have a variety of manifestations. The anemia can range from mild to severe, with associated hyperbilirubinemia and jaundice. In severe cases, hemolysis may lead to extramedullary hematopoiesis and reticuloendothelial clearance of fetal RBCs, which may result in hepatosplenomegaly, decreased liver function, hypoproteinemia, ascites, and anasarca. When accompanied by high-output cardiac failure and pericardial effusion, this condition is known as hydrops fetalis. Without intervention it is often fatal. Intensive neonatal care, including emergent exchange transfusion, is required.

Cases of hemolysis in the newborn that do not result in fetal hydrops can still lead to kernicterus, a neurologic condition observed in infants with severe hyperbilirubinemia due to the deposition of unconjugated bilirubin in the brain. Symptoms that manifest several days after delivery can include poor feeding, inactivity, loss of the Moro reflex, bulging fontanelle, and seizures. The 10% of infants who survive may develop spastic choreoathetosis, deafness, and/or mental retardation.

Hemolytic disease in the fetus or newborn was once a major contributor to perinatal morbidity and mortality. However, the widespread use of antenatal and postpartum RhD immunoglobulin in developed countries has resulted in a major decrease in the frequency of this disease. In developing countries without prophylaxis programs, stillbirth occurs in 14% of affected pregnancies, and 50% pregnancy survivors either die in the neonatal period or develop cerebral injury.\(^3\)

**Prevention of Alloimmunization**

There are 4 RhD immunoglobulin products available in the United States, all of which undergo micropore filtration to eliminate viral transmission.\(^3\) To date, no reported cases of viral infection related to RhD immunoglobulin administration have been reported in the United States.\(^3\) Theoretically, the Creutzfeldt-Jakob disease agent could be transmitted by use of RhD
immunoglobulin. Local adverse reactions may occur including redness, swelling and mild pain at the site of injection, and hypersensitivity reactions.

The American College of Obstetricians and Gynecologists and the American Association of Blood Banks recommend the first dose of Rh\(_0\)(D) immunoglobulin (eg, RhoGAM) be given at 28 weeks of gestation (or earlier if there's been an invasive event), followed by a postpartum dose given within 72 hours of delivery.

**Diagnosis of Alloimmunization**

The diagnosis of alloimmunization is based on detection of anti-RhD antibodies in the maternal serum. The most common test for determining antibodies in serum is the indirect Coombs test. Maternal serum is incubated with known RhD-positive RBCs. Any anti-RhD antibody present in the maternal serum will adhere to the RBCs. The RBCs are then washed and suspended in Coombs serum, which is antihuman globulin. RBCs coated with maternal anti-RhD will agglutinate, which is referred to as a positive indirect Coombs test. The indirect Coombs titer is the value used to direct management of pregnant alloimmunized women.

**Management of Alloimmunization During Pregnancy**

A patient’s first alloimmunized pregnancy involves minimal fetal or neonatal disease. Subsequent pregnancies are associated with more severe degrees of fetal anemia. Treatment of an alloimmunized pregnancy requires monitoring of maternal anti-D antibody titers and serial ultrasound assessment of middle cerebral artery peak systolic velocity of the fetus.

If severe fetal anemia is present near term, delivery is performed. If severe anemia is detected remote from term, intrauterine fetal blood transfusions may be performed.

**Determining Fetal RhD Status**

The American College of Obstetrician and Gynecologists has recommended that all pregnant women be tested during their first prenatal visit for ABO blood group typing and RhD type, and be screened for the presence of anti-RBC antibodies. These laboratory tests should be repeated for each subsequent pregnancy. The American Association of Blood Banks has also recommended that antibody screening be repeated before administration of anti-D immune globulin at 28 weeks of gestation, postpartum, and at the time of any event during pregnancy.
If the mother is determined to be RhD-negative, the paternal RhD status should also be determined at the initial management of a pregnancy. If paternity is certain and the father is RhD-negative, the fetus will be RhD-negative, and further assessment and intervention are unnecessary. If the father is RhD-positive, he can be either homozygous or heterozygous for the D allele. If homozygous for the D allele (ie, D/D), then the fetus is RhD-positive. If the paternal genotype is heterozygous for Rh status or is unknown, determination of the RhD status of the fetus is the next step to assess the RhD compatibility of the pregnancy (either first or any subsequent pregnancy).

Invasive and noninvasive testing methods to determine the RhD status of a fetus are available. These procedures use polymerase chain reaction (PCR) assays to assess the fetal cellular elements in amniotic fluid by amniocentesis or by chorionic villus sampling (CVS). Although CVS can be performed earlier in a pregnancy, amniocentesis is preferred because CVS is associated with disruption of the villi and the potential for larger fetomaternal hemorrhage and worsening alloimmunization if the fetus is RhD-positive. The sensitivity and specificity of fetal RHD genotyping by PCR by polymerase chain reaction are reported as 98.7% and 100%, respectively, with positive and negative predictive values of 100% and 96.9%, respectively.¹

Noninvasive testing involves molecular analysis of cell-free fetal DNA (cffDNA) in the maternal plasma or serum. In 1998, Lo et al showed that about 3% of cffDNA in the plasma of first trimester pregnant women is of fetal origin, with this percentage rising to 6% in the third trimester.⁵ Fetal DNA cannot be separated from maternal DNA, but if the pregnant woman is RhD-negative, the presence of specific exons of the RHD gene, which are not normally present in the circulation of an RhD-negative patient, predicts an RhD-positive fetus. Cell-free fetal DNA has been proposed as a noninvasive alternative to obtaining fetal tissue by invasive methods, which are associated with a risk of miscarriage.¹

The large quantity of maternal DNA compared with fetal DNA in the maternal circulation complicates the inclusion of satisfactory internal controls to test for successful amplification of fetal DNA. Therefore, reactions to detect Y chromosome-linked gene(s) can be included in the test, which will be positive when the fetus is a male.¹ When Y chromosome-linked genes are not detected, tests for variants may be performed to determine whether the result is derived from fetal, not maternal, DNA.

Cell-free fetal DNA testing to determine the fetal RHD genotype is standard of care in many European countries.³
Summary of Evidence

For individuals who are pregnant and have 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, which is 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 will lead to improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in March 2018 did not identify any ongoing or unpublished phase 3 trials that would likely influence this review.

Practice Guidelines and Position Statements

American Association of Blood Banks

The American Association of Blood Banks has not issued specific practice guidelines or recommendations on the use of fetal Rhesus D (RHD) genotyping.

American College of Obstetricians and Gynecologists

In 2018, the American College of Obstetricians and Gynecologists reaffirmed its 2006 position that detection of fetal 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.”

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. 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.

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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 SensiGene™ Fetal RHD Genotyping test, performed by proprietary SEQureDx™ 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 the uses of its test include:

- Clarifying fetal RhD status without testing the father, 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

References

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<tr>
<th>Date</th>
<th>Comments</th>
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<td>12/09/13</td>
<td>New Policy. New policy developed with review of the literature through October 6, 2013. Fetal RHD genotyping using maternal plasma is considered investigational.</td>
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<td>01/13/15</td>
<td>Annual Review. Policy updated with literature review through September 26, 2014. Added name of commercially available next generation sequencing test to the Policy Guidelines. References 6 and 7 added; others renumbered. Policy statement unchanged. Remove ICD-9 and ICD-10 diagnosis codes; these are not utilized in policy adjudication.</td>
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<td>01/12/16</td>
<td>Annual review. Policy updated with literature review; policy statement unchanged. Part of pilot formatting test group.</td>
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