Fetal RHD Genotyping Using Maternal Plasma

Effective: August 1, 2017

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

The use of cell-free fetal DNA in maternal blood has been proposed as a noninvasive method to determine fetal RHD genotype.

MEDICAL POLICY CRITERIA

Fetal RHD genotyping using maternal plasma is considered investigative.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Sequencing-based Tests to Determine Fetal Aneuploidies and Microdeletions from Maternal Plasma DNA, Genetic Testing, Policy No 44

BACKGROUND

Rhesus (Rh) D-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 Rh status of the fetus may guide subsequent management of the pregnancy.
The use of cell-free fetal DNA in maternal blood has been proposed as a noninvasive method to determine fetal RHD genotype.

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

**RH BLOOD GROUPS**

The (Rhesus) Rh 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 autosomal 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 (i.e., they lack the *RHD* gene and the corresponding RHD antigen).

RHD-negative status varies among ethnic group and is 15% in whites, 5 to 8% in African Americans, 5% to 8%, and 1 to 2% in Asians and Native Americans, respectively.

In the Caucasian population, almost all RHD-negative individuals are homozygous for a deletion of the *RHD* gene. However, in the African-American population, only 18% of RHD-negative individuals are homozygous for an RHD deletion, and 66% of RHD-negative African Americans have an inactive RHD pseudogene (RHDy).[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.

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 red blood cell (RBC) membrane, and alloimmunization can be caused when fetal Rh-positive RBCs enter maternal circulation, and the Rh-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 ~10% of pregnancies are Rh-
incompatible, <20% of Rh-incompatible pregnancies actually lead to maternal alloimmunization.

Small feto-maternal hemorrhages of RHD-positive fetal RBCs into the circulation of an RHD-negative woman occurs in nearly all pregnancies, and percentages of feto-maternal 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 to 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 (e.g., amniocentesis), in utero 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

IgG 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, which without intervention, 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.

The result of disease from alloimmunization, hemolytic disease of the fetus or newborn, was once a major contributor to perinatal morbidity and mortality. However, with the widespread adoption of antenatal and postpartum use of Rh immune globulin in developed countries, the result has been a major decrease in frequency of this disease. In developing countries without prophylaxis programs, stillbirth occurs in 14% of affected pregnancies, and 50% of pregnancy survivors either die in the neonatal period or develop cerebral injury.[3]

PREVENTION OF ALLOIMMUNIZATION

There are four currently in use Rh immune globulin products available in the U.S., all of which undergo micropore filtration to eliminate viral transmission.[3] To date, no reported cases of viral infection related to Rh immune globulin administration have been reported in the U.S.[3] Theoretically, the Creutzfeldt-Jakob disease (CJD) agent could be transmitted by use of Rh immune globulin. Local adverse reactions may occur, including redness, swelling, and mild pain at the site of injection, and hypersensitivity reactions have been reported.

The American College of Obstetricians and Gynecologists (ACOG) and the American Association of Blood Banks (AABB) recommend the first dose of Rh(D) immune globulin (e.g.,
RhoGAM®) be given at 28 weeks’ 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.[2] 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**

ACOG recommends that all pregnant women should be tested at the time of their first prenatal visit for ABO blood group typing and Rh-D type and be screened for the presence of anti-RBC antibodies. These laboratory tests should be repeated for each subsequent pregnancy. The AABB also recommends that antibody screening be repeated before administration of anti-D immune globulin at 28 weeks’ gestation, postpartum, and at the time of any event during pregnancy.

If the mother is determined to be Rh-negative, the paternal Rh status should also be determined at the initial management of a pregnancy. If paternity is certain and the father is Rh-negative, the fetus will be Rh-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 he is homozygous for the D allele (i.e., D/D) then the fetus is RHD-positive. If the paternal genotype is heterozygous for Rh status or is unknown, determination of the Rh-status of the fetus is the next step.

Invasive and noninvasive testing methods to determine the Rh status of a fetus are available.

Invasive 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 the preferred method 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 typing by PCR are reported as 98.7% and 100%, respectively, with positive and negative predictive values of 100% and 96.9%, respectively.[4]
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 cell-free DNA 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 to 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 polymorphisms may be performed to determine whether the result is derived from fetal but not maternal DNA.

**REGULATORY STATUS**

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 (y) pseudogene in exon 4, and assay controls which are 3 targets on the Y chromosome (SRY, TTTY, DBY).

The company claims that the uses of its test include:

- Clarify fetal RHD status without testing the father, which would avoid the cost of paternity testing and paternal genotyping.
- Clarify fetal RHD status when maternal anti-D titers are unclear.
- Identify the RHD (-) fetus in mothers who are opposed to immunization(s) and vaccines.
- RHD (-) sensitized patients, which would avoid invasive testing by CVS or genetic amniocentesis.

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

**EVIDENCE SUMMARY**

Fetal RHD genotyping is best evaluated in the framework of a diagnostic test, as the test provides diagnostic information that assists in treatment decisions. Validation of the clinical use of any diagnostic test focuses on 3 main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

ANALYTIC VALIDITY

No studies were identified that provide direct evidence of the analytic validity of RHD genotyping. The commercially available test uses next-generation sequencing. Neither the routine quality control procedures used for the test, nor the analytic performance metrics have been published.

CLINICAL VALIDITY

Systematic Reviews

In 2017, Mackie et al. published a systematic review and meta analysis of studies on the diagnostic accuracy of cell-free fetal DNA-based non-invasive prenatal testing.[6] Thirty of the 117 included cohort studies in the analysis evaluated RHD status. The overall sensitivity and specificity were 99.3% and 98.4% respectively. Real-time PCR exhibited higher sensitivity when compared to conventional PCR. There was no difference in specificity. Ten of the 30 studies reported inconclusive results.

In 2014, Zhu et al. published a meta-analysis of studies on the diagnostic accuracy of noninvasive fetal RHD genotyping using cell-free fetal DNA.[7] The investigators identified 37 studies conducted in RHD-negative pregnant women that were published by the end of 2013. The studies included a total of 11,129 samples, and 352 inconclusive samples were excluded. When all data were pooled, the sensitivity of fetal RHD genotyping was 99% and the specificity was 98%. Diagnostic accuracy was higher in samples collected in the first trimester (99.0%) than those collected in the second (98.3%) or third (96.4%) trimesters.

Nonrandomized Studies

A 2014 prospective study by Chitty et al. was published after the Zhu meta-analysis.[8] Samples from 2,288 Rh-negative women who initiated prenatal care before 24 weeks of gestation were analyzed using RHD genotyping. Overall, the sensitivity of the test was 99.34% and the specificity was 94.91%. The likelihood of correctly detecting RHD status in the fetus increased with gestational age, with high levels of accuracy after 11 weeks. For example, for samples taken before 11 completed weeks of gestation, the sensitivity was 96.85% and the specificity was 94.40%, and at 14-17 weeks’ gestation, sensitivity was 99.67% and specificity was 95.34%. These findings of increased accuracy as pregnancies advanced differ from that of the Zhu meta-analysis which found highest diagnostic accuracy in the first trimester.

Picchiassi et al. studied whether the amount of DNA sample analyzed increased sensitivity.[9] Real-time PCR (qPCR) was performed on two groups, group 1 with 95 plasma aliquots that were available from first trimester blood collection and group 2 with 13 samples collected between 18 and 25+6 weeks’ gestation. qPCR was repeated to increase each sample amount. While diagnostic accuracy increase in groups 1 and 2, the change was not statistically significant (90.5% to 93.7% and 84.6% to 92.3%, respectively)

A study published in 2012 by Wikman et al. reported the results of a prospective, population-based study involving 4118 RHD-negative, nonalloimmunized pregnant women from 83 maternity care centers.[10] Median gestational age was 10 weeks (range, 3-40 weeks), with
75.5% of patients undergoing testing in the first trimester, 18.8% in the second, 4.3% in the third, and 1.4% unknown. Extracted DNA samples from each woman were analyzed in triplicate. Reanalysis had to be performed in 211 (5.1%) cases with inconclusive results in the first analysis. A positive or negative fetal RHD was reported for 96% of the samples, with 165 (4%) remaining inconclusive. A second sample was then obtained from 147 of the 165 pregnancies with inconclusive results: 14 (0.8%) remained inconclusive, all resulting from a weak or silent maternal RHD gene. Blood group serology of the newborns was used as the gold standard, and blood group serology results were missing for 466 pregnancies, leaving 3652 newborns for whom the validity of RHD genotyping could be assessed. The false-negative rate (RHD genotyping was Rh-negative, but newborn was determined to be Rh-positive) was 55 of 2297 (2.4%) and the false-positive rate (RHD genotyping was Rh-positive, but newborn was determined to be Rh-negative) was 15 of 1355 (1.1%). After exclusion of the samples obtained before the 8th week of gestation, the false-negative rate was 23 of 2073 (1.1%) and the false-positive rate was 14 of 1218 (1.1%). Both sensitivity and specificity were close to 99% if the samples were not collected before gestational week 8. The authors note that a limitation of their study was the lack of a positive control for fetal DNA.

In 2012, Moise and colleagues analyzed samples from 120 patients who were enrolled prospectively between May 2009 and July 2010 from multiple centers. All patients were Rh-negative pregnant patients with no evidence of alloimmunization. Race/ethnicity was Caucasian/white (72.5%), African-American/black (12.5%), Hispanic/Latino (12.5%), Asian (0.8%), and other (1.7%). The samples were analyzed using the SensiGENE RHD test using MALDI-TOF mass spectrometry to detect control and fetal-specific DNA signals. The determination of fetal sex was: 3 Y-chromosome markers=male fetus, 2 markers=inconclusive, and 1 or no markers=female fetus. The algorithm for RHD determination was: pseudogene present=inconclusive, 3 RHD markers present=RHD-positive fetus, 2 markers present=inconclusive, 1 or no markers= RHD-negative fetus. The pregnant patients underwent planned venipunctures during 3 time periods in gestation: 11–13 6/7, 16–19 6/7, and 28–29 6/7 weeks. Median gestational age of the first, second and third trimester samplings was 12.4 (range, 10.6–13.9) weeks, 17.6 (16–20.9) weeks and 28.7 (27.9–33.9) weeks, respectively. Twenty-two samples (6.3% of the total samples; 2.5% of the patients) were deemed inconclusive. In 23% of these inclusive cases, there was an RHD-negative, female result, but there were an insufficient number of paternal SNPs detected to confirm the presence of fetal DNA. In the remaining 77% of the inconclusive results (4.8% of the total samples), the RHD psi (y)-pseudogene was detected, and the sample was deemed inconclusive. Erroneous results were observed for 6 of the samples (1.7%), and included discrepancies in 4 RHD typings (1.1%) and 2 fetal sex determinations (0.6%) following data unblinding. Three cases of RHD typing were false positives (ccffDNA was RHD-positive but neonatal serology RHD-negative) and one case was a false negative (ccffDNA: RHD-negative but neonatal serology RHD-positive). Accuracy for determination of the RHD status of the fetus was 99.1%, 99.1%, and 98.1%, respectively for each of the 3 consecutive trimesters of pregnancy, and accuracy of fetal sex determination was 99.1%, 99.1%, and 100%, respectively. The authors note, “the current test has not been validated for its ability to predict the zygosity of the fetus when the psi-pseudogene is detected because of limited number of pseudogene cases in conjunction with the challenge of assessing limited fetal copies against the high background of maternal DNA.”

In 2011, Bombard and colleagues analyzed the performance of the SensiGene Fetal RHD test in 2 cohorts using a retrospective study design. Cohort 1 used as a reference point the clinical RHD serotype obtained from cord blood at delivery. Samples from cohort 2 were originally
In cohort 1, \textit{RHD} genotyping was performed on 236 maternal plasma samples from singleton, nonsensitized pregnancies with documented fetal RHD serology. The samples were obtained at 11-13 weeks’ gestation. Ethnic origin of the pregnant women was Caucasian 77.1\%, African 19.1\%, mixed race 3.4\% and South Asian (0.4\%). Neonatal RHD phenotype, determined by serology at the time of birth, was positive in 69.1\% of samples and negative in 30.9\% of samples. In 2 (0.9\%) of the 236 samples, there the results were classified as invalid. In the 234 (99.1\%) samples with sufficient DNA extraction, the result was conclusive in 207 samples (88.5\%); inconclusive in 16 samples (6.8\%); and psi (+)/RHD variant in 11 samples (4.7\%). In the 207 samples with a conclusive result, the neonatal RHD phenotype was positive in 142 samples (68.6\%) and negative in 65 samples (31.4\%). The RHD Genotyping test correctly predicted the neonatal RHD phenotype in 201 of 207 samples for an accuracy of 97.1\% (95\% confidence interval [CI], 93.5 to 98.8). In the 142 samples with RHD-positive fetuses, the test predicted that the fetus was positive in 138 and in 4 that it was negative, for a sensitivity of prediction of RHD positivity of 97.2\% (95\% CI, 93.0 to 98.9). In 63 of the 65 samples with RHD-negative fetuses, the RHD Genotyping test predicted that the fetus was negative and, in the remaining 2, that it was positive, for a specificity for the prediction of RHD positivity of 96.9\% (95\% CI, 89.5 to 99.1). The test predicted that the fetus was RHD-positive in 140 samples, of which, in 138 of these the prediction was correct, for a positive predictive value of 98.6\% (95\% CI, 94.9 to 99.6). The test predicted that the fetus was RHD-negative in 67 samples, of which, in 63 of these the prediction was correct, for a negative predictive value for RHD-positive fetuses of 94.0\% (95\% CI, 85.6 to 97.6). Cohort 1 samples were limited in the amount of sample available for analysis.

Cohort 2 consisted of 205 samples from 6-30 weeks’ gestation. Testing was for the presence of \textit{RHD} exon sequences 4, 5, 7, the psi-pseudogene, and 3 Y-chromosome sequences (SRY, DBY and TTTY2), using MALDI-TOF MS-(the RHD Genotyping laboratory developed test). The laboratory performing the assays for both cohorts was blinded to the sex and fetal RHD genotype. In cohort 2, the test correctly classified 198 of 199 patients, for a test accuracy of 99.5\%, with a sensitivity and specificity for prediction of RHD genotype of 100.0\% and 98.3\%, respectively.

Recent literature replicates previous findings that fetal RHD genotyping can be accurately determined using cell-free fetal DNA from maternal plasma, although not all Rh-positive fetuses are identified.[13-18]

**CLINICAL UTILITY**

No published data are identified showing that this type of testing leads to improved health outcomes. This type of testing could lead to the avoidance of the use of anti-D immune globulin (e.g., RhoGAM) in Rh-negative mothers with Rh-negative fetuses. However, the false negative rate of the test, which is low, is not zero, and a certain percentage of Rh-negative women will develop alloimmunization to Rh-positive fetuses. Other issues that still need to be defined include the optimal timing of testing during the pregnancy.

**SECTION SUMMARY**

The clinical validity of fetal RHD genotyping is high, in that the test has shown a high degree of accuracy in correctly predicting fetal RHD status. However, the test does not identify all Rh-
positive fetuses, which may lead to alloimmunization of the Rh-negative mothers in these cases. The current data that demonstrates how the results from cell-free fetal DNA analysis in maternal blood are used to alter treatment decisions and improve health outcomes compared to conventional testing are lacking. Therefore, the clinical utility of fetal RHD genotyping is unknown, and it is uncertain whether it will lead to improved health outcomes.

**PRACTICE GUIDELINE SUMMARY**

**AMERICAN ASSOCIATION OF BLOOD BANKS (AABB)**

AABB does not have specific practice guidelines or recommendations on the use of fetal RHD genotyping.

**AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG)**

ACOG does not have specific practice guidelines or recommendations on the use of fetal RHD genotyping.

**SUMMARY**

More research is needed to know how well fetal RHD genotyping with maternal plasma works for improving health outcomes compared to current standard of care. No clinical guidelines based on research recommend fetal RHD genotyping with maternal plasma. Therefore, fetal RHD genotyping using maternal plasma is considered investigational.

**REFERENCES**

2. Moise, K. Overview of Rhesus (Rh) alloimmunization in pregnancy. 2013. PMID:

**CODES**

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<td>Molecular pathology procedure, Level 4 RHD (<em>Rh blood group, D antigen</em>) (eg, hemolytic disease of the fetus and newborn, Rh maternal/fetal compatibility), deletion analysis (eg, exons 4, 5 and 7, pseudogene), performed on cell-free fetal DNA in maternal blood (For human erythrocyte gene analysis of RHD, use a separate unit of 81403)</td>
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