NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

High-throughput, non-invasive prenatal testing (NIPT) for fetal rhesus D status

Final scope

November 2015

1 Introduction

The Medical Technologies Advisory Committee identified high-throughput, non-invasive prenatal testing for fetal rhesus D status as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. The revised scope was informed by discussions at the scoping workshop held on 13 October 2015 and the assessment subgroup meeting held on 27 October 2015. A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technology

This section describes the properties of the diagnostic technology based on information provided to NICE by the International Blood Group Reference Laboratory and clinical experts. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

High-throughput, non-invasive prenatal testing (NIPT) for fetal rhesus D (RhD) status involves analysing cell-free fetal DNA in maternal blood. It is intended for use in all pregnant people who are RhD negative and who are not known to be sensitised to the RhD antigen.

Human red blood cells carry many antigens on their surfaces. People with the RhD antigen are referred to as RhD positive, and those without the antigen as RhD negative. A baby inherits its blood type from both parents, therefore a pregnant person who is RhD negative can carry a baby who is RhD positive. During pregnancy small amounts of fetal blood can enter the maternal circulation (an event called feto-maternal haemorrhage). The presence of fetal RhD-positive cells in the maternal circulation can cause a mother who is RhD

negative to produce antibodies against the RhD antigen (anti-D antibodies). This process is called sensitisation.

Sensitisation can happen at any time during pregnancy, but is most common in the third trimester and during childbirth. Sensitisation can follow events in pregnancy known to be associated with feto-maternal haemorrhage, such as medical interventions (chorionic villus sampling, amniocentesis or external cephalic version), terminations, late miscarriages, antepartum haemorrhage and abdominal trauma. These are called potentially sensitising events.

The process of sensitisation has no adverse health effects for the mother and usually does not affect the pregnancy during which it occurs. However, if the mother is exposed to the RhD antigen (from a RhD positive fetus) during a subsequent pregnancy, the immune response is quicker and much greater. The anti-D antibodies produced by the mother can cross the placenta and cause haemolytic disease of the fetus and newborn.

The risk of sensitisation can be reduced by administering anti-D immunoglobulin to pregnant people who are RhD negative. Anti-D immunoglobulin is recommended for all pregnant people who are RhD negative, as the RhD status of the baby is unknown. Anti-D immunoglobulin is produced from pooled plasma from large numbers of RhD negative donors who have been transfused with RhD positive red cells to stimulate the production of RhD antibodies, and thus carries a small risk of transmission of human blood-borne viral or prion diseases. The National Comparative Audit of Blood Transfusion: 2013 Audit of anti-D immunoglobulin prophylaxis indicates that of the people eligible for anti-D immunoglobulin, 99.0% had anti-D immunoglobulin. Of the eligible people who declined anti-D immunoglobulin, 42% declined for reasons other than the father being RhD negative.

High-throughput, NIPT for fetal RhD status may enable anti-D immunoglobulin to be withheld from people who are RhD negative and carrying a RhD negative fetus. These people could avoid unnecessary treatment with anti-D immunoglobulin, along with the slight risk associated with blood products. In addition, these people may not need testing following potentially sensitising events and birth.

High-throughput, NIPT for fetal RhD status may allow people who are RhD negative and carrying a RhD positive fetus to make an informed choice about whether to have treatment with anti-D immunoglobulin. This may lead to better compliance with anti-D immunoglobulin treatment as these people know that the risk of sensitisation is high. This may reduce the number of sensitisations and hence, haemolytic disease of the fetus and newborn in subsequent pregnancies.

2.2 Product properties

High-throughput, NIPT for fetal RhD status uses a real time quantitative polymerase chain reaction (PCR) method for determining fetal RhD genotype from fetal DNA in the plasma of people who are RhD negative. It is an in-house test which is available as a test service from the International Blood Group Reference Laboratory, NHS Blood and Transplant, Bristol. The laboratory is CPA accredited and participates in sample exchange organised by the International Society of Blood Transfusion.

The test principle is based on analysis of cell-free fetal DNA - small fragments of fetal DNA shed from the placenta that circulate freely in the maternal blood plasma. The cell-free fetal DNA only circulates during pregnancy and is rapidly cleared from the maternal circulation after delivery. Levels of cell-free fetal DNA in maternal blood increase throughout the pregnancy, and studies have reported that fetal RhD genotyping is accurate for the prediction of RhD status if it is performed from 11 weeks' gestation. A person who is RhD negative does not carry a copy of the RHD gene so the presence of an RHD gene in a pregnant person who is RhD negative suggests a RhD positive fetus.

The test is performed on 4 ml to 6 ml of maternal anti-coagulated blood. DNA is extracted using an automated robotic platform (MDx BioRobot, Qiagen) which has a capacity of 88 samples per run. The robotic platform is also used as a liquid handler to dispense samples and reagents, and PCR is performed on an ABI Prism 7900HT analyser (Applied Biosystems). Primers and probes for exons 5 and 7 of the RHD gene are used, and the following controls are tested alongside the samples: RhD positive DNA, RhD negative DNA, RHD pseudogene positive DNA, and no DNA. Samples are tested in batches of between 32 and 88 samples. The time to complete the test from sample receipt to report generation is 5 to 6 hours, depending on the size of the batch. An algorithm is used to determine the fetal RhD status and results are reported as RhD positive, RhD negative, or indeterminate – treat as RhD positive. It is claimed that the test can be performed by a band 4 Biomedical Scientist.

3 Target condition

3.1 Rhesus D

About 16% of the white British population are RhD negative and usually have no copies of the RHD gene. People who are RhD positive have either one or two copies of the RHD gene. Many variants of the RHD gene exist: in some people, all or part of RHD gene is present but no RhD antigen is expressed; in

others, part of the RHD gene is absent but a variant form of RhD antigen is present. RHD gene variants are relatively rare in white people (less than 1% of all RhD negative people). In people of African and Caribbean family origin, about 9% are RhD negative. An inactive RHD gene, called the RHD pseudogene, is present in 66% of this group (Finning et al. 2008).

From April 2013 to March 2014 there were 646,904 births in England (NHS Maternity Statistics), of which approximately 15% (97,036) were to people who are RhD negative. About 40% of these people carry a RhD negative fetus (around 39,000 per year), and therefore do not need treatment with anti-D immunoglobulin.

3.2 Haemolytic disease of the fetus and newborn

In mothers who are RhD negative and have been sensitised to the RhD antigen, a subsequent pregnancy with a RhD positive fetus will cause an immune response in the mother. The anti-D antibodies produced by the mother cross the placenta and bind to RhD antigen on the surface of fetal red blood cells. These antibody-coated fetal red blood cells are removed from the fetal circulation and fetal anaemia results if the red blood cells are removed faster than they are produced. Severe anaemia can lead to fetal heart failure, fluid retention and swelling (hydrops), and intrauterine death. This is known as haemolytic disease of the fetus and newborn.

When red blood cells are broken down, bilirubin is released. In utero this is cleared by the placenta and is not harmful. However, after birth the neonatal liver cannot cope with the excess production of bilirubin, and this leads to jaundice. Low levels of jaundice are not harmful but, if left untreated, higher levels can result in damage to specific areas of the neonatal brain, causing permanent brain damage. This can lead to a range of neurodevelopmental problems, such as cerebral palsy, deafness, and motor and speech delay.

Anti-D immunoglobulin is given to pregnant people who are RhD negative to prevent sensitisation. Anti-D immunoglobulin is produced from male donors with a RhD negative blood group who are given small amounts of RhD positive blood to produce an antibody reaction. These males can then donate their blood at regular intervals and the antibodies can be extracted from the plasma. A single dose of anti-D immunoglobulin will involve blood from multiple donors. Anti-D immunoglobulin is therefore a scarce commodity, and conservation of stocks is important. Treatment with anti-D immunoglobulin is associated with the possibility of blood-borne infection. However, the production of anti-D immunoglobulin is strictly controlled, with procedures in place to ensure that the chance of a virus being passed from the donor to the person receiving the anti-D immunoglobulin is very low.

Before anti-D immunoglobulin was available, the incidence of RhD sensitisations in people who are RhD negative following the birth of 2 RhD positive babies was approximately 16%. Haemolytic disease of the fetus and newborn was a significant cause of morbidity and mortality, occurring in approximately 1% of all births. Since the introduction of routine post-partum administration of anti-D immunoglobulin, the rate of sensitisations dropped to approximately 2%. A further reduction in the sensitisation rate ranging from 0.17% to 0.28% was achieved after the introduction of routine antenatal prophylaxis during the third trimester of pregnancy. Associated with this reduction in sensitisations was a reduction in mortality associated with haemolytic disease of the fetus and newborn, from 46 in 100,000 births to 1.6 in 100,000 births (British Committee for Standards in Haematology 2014).

3.3 Patient issues and preferences

A 2013 audit of anti-D immunoglobulin prophylaxis found that 131 of 5972 pregnant people who are RhD negative declined anti-D immunoglobulin. If NIPT for fetal RhD status is performed, pregnant people who are RhD negative and are identified as having an RhD positive fetus through NIPT would be able to make an informed choice about whether or not to have anti-D immunoglobulin. Pregnant people who are RhD negative and are identified as having a RhD negative fetus through NIPT would gain the knowledge that the mother is not at risk of sensitisation. This may reduce anxiety for the family and the mother can avoid having unnecessary anti-D immunoglobulin.

3.4 Diagnostic and care pathway

3.4.1 Pregnant people who are RhD negative and not sensitised to RhD antigen

The NICE guideline on antenatal care (2008) recommends that people should be offered testing for blood group and rhesus D status in early pregnancy. All people identified as RhD negative would be tested for the presence of RhD antibodies, regardless of whether they are known to be sensitised or not. In people identified as RhD negative who do not have RhD antibodies present, anti-D immunoglobulin is recommended, both as prophylaxis and following potential sensitising events, to prevent sensitisation occurring.

The NICE technology appraisal on routine antenatal anti-D prophylaxis for people who are rhesus D negative (2008) recommends routine antenatal anti-D prophylaxis as a treatment option for all pregnant people who are RhD negative and who are not known to be sensitised to the RhD antigen. Routine antenatal anti-D prophylaxis can be given as 2 doses at weeks 28 and 34 of pregnancy, or as a single dose between 28 and 30 weeks.

Additionally, the British Committee for Standards in Haematology (BCSH) guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn (2013) recommend that:

- Following potentially sensitising events, anti-D immunoglobulin should be administered as soon as possible and always within 72 hours of the event. Appropriate tests for feto-maternal haemorrhage should be carried out for all RhD negative, previously non-sensitised, pregnant people who have had a potentially sensitising event after 20 weeks of gestation.
- Routine antenatal anti-D prophylaxis should be regarded as a separate entity and administered regardless of, and in addition to, any anti-D immunoglobulin that may have been given for a potentially sensitising event.
- Following birth, ABO and RhD typing should be performed on cord blood. If the baby is confirmed to be RhD positive, all RhD negative, previously non-sensitised, people should be offered anti-D immunoglobulin within 72 hours following delivery. Maternal samples should be tested for feto-maternal haemorrhage and additional dose(s) given as guided by feto-maternal haemorrhage tests.

The NICE guideline on ectopic pregnancy and miscarriage (2012) recommends that anti-D prophylaxis is offered to all people who are RhD negative who have a surgical procedure to manage an ectopic pregnancy or a miscarriage.

3.4.2 Pregnant people who are RhD negative and are sensitised to RhD antigen

The Royal College of Obstetricians and Gynaecologists have published guidance on the management of people with red cell antibodies during pregnancy (2014). This guideline recommends that all people who are RhD negative and are sensitised to RhD antigen should:

- attend for pre-pregnancy counselling with a clinician with knowledge and expertise of this condition,
- have their blood group and antibody status determined at the booking appointment (ideally by 10 weeks of gestation) and at 28 weeks of gestation,
- be offered non-invasive fetal RhD genotyping using maternal blood if maternal RhD antibodies are present.

If a RhD positive fetus is identified, additional monitoring and treatment are required during the pregnancy. The guideline recommends:

- measurement of RhD antibody levels every 4 weeks up to 28 weeks of gestation and then every 2 weeks until delivery,
- referral to a fetal medicine specialist if there are rising RhD antibody levels/titres, a level/titre above a specific threshold or ultrasound features suggestive of fetal anaemia,
- weekly monitoring by ultrasound if RhD antibody levels/titres rise above a specific threshold.
- fetal blood sampling if ultrasound shows signs of fetal anaemia, and consideration of intrauterine transfusion.
- consideration of early delivery of the baby; dependent on antibody levels/titres and whether any fetal therapy has been required.
- use of continuous electronic fetal heart monitoring during labour.

Once the baby is born, the guideline recommends:

- cord blood samples are taken for a direct antiglobulin test, tests for haemoglobin (anaemia) and bilirubin levels (jaundice), and to confirm the blood group of the baby
- regular clinical assessment of the baby's neurobehavioural state and observations for the development of jaundice and/or anaemia
- regular assessment of bilirubin and haemoglobin levels.

The NICE guideline on neonatal jaundice (2010) recommends that serum bilirubin level is measured in all babies with suspected or obvious jaundice. Serum bilirubin should then be measured every 6 hours until the level is below the treatment threshold and is stable or falling. Dependent on the bilirubin levels, a baby with jaundice may be treated with phototherapy. If the serum bilirubin continues to rise, treatment with intravenous immunoglobulin is used alongside phototherapy. If the bilirubin levels remain high, an exchange blood transfusion may be required.

4 Scope of the evaluation

Table 1: Scope of the evaluation

Decision question	Does high throughput NIPT for fetal RhD status represent a clinically and cost-effective use of NHS resources?
Populations	Pregnant people who are RhD negative and are not sensitised to RhD antigen
Intervention	High throughput, NIPT for fetal rhesus D status (International Blood Group Reference Laboratory, Bristol)

Comparator	The comparator for the economic model is no testing. The gold standard for assessing the accuracy of high-throughput, NIPT for fetal RhD status is testing of cord blood.
Healthcare setting	All settings
Outcomes	Intermediate measures for consideration may include: • Accuracy • Number of indeterminate results (owing to technical reasons and genetic variants) • Number of pregnant people who are RhD negative and not sensitised who accept the test • Number of doses of anti-D immunoglobulin given (routine antenatal, following potentially sensitising events and postnatal) • Compliance with anti-D (antenatal and postnatal) immunoglobulin
	Clinical outcomes for consideration may include: • Number of infections from anti-D immunoglobulin • Adverse effects from anti-D immunoglobulin • Number of sensitisations • Number of cases of haemolytic disease of the fetus and newborn in subsequent pregnancies
	Patient-reported outcomes for consideration may include: • Health related quality of life including anxiety
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of high throughput, NIPT for fetal RhD status • Cost of testing following potentially sensitising events • Anti-D immunoglobulin, associated administration costs and treatment of any adverse effects • Costs of post-delivery testing • Cost of hospital stay following birth (length of stay) • Costs of managing future pregnancies when sensitisation has occurred • Costs associated with treatment of haemolytic disease of the fetus and newborn
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

5 Modelling approach

The aim and structure of the economic model will depend upon the final scope.

5.1 Existing models

Three relevant economic models were identified:

Szczepura et al. (2011) conducted an economic analysis of NIPT for fetal RhD status in England and Wales. Two scenarios were considered. In the first, NIPT was used to target antenatal anti-D prophylaxis with cord blood typing used to guide post-delivery anti-D prophylaxis. In the second scenario, NIPT was used to target antenatal anti-D prophylaxis and to guide post-delivery anti-D prophylaxis. Both scenarios were compared with routine antenatal anti-D prophylaxis for all and post-delivery prophylaxis guided by cord blood typing. Results show that if NIPT is used to target antenatal prophylaxis and cord blood typing is used to direct post-delivery prophylaxis, no savings would be seen compared with routine prophylaxis for all. However, if NIPT used to target antenatal prophylaxis and to direct post-delivery prophylaxis, expected savings are £507,154 per year compared with routine prophylaxis for all, with 1 additional sensitisation for every £9190 saved.

Hawk et al. (2013) examined the costs of NIPT for fetal RhD status in the United States. Authors compared use of NIPT for fetal RhD status to guide antenatal and post-delivery anti-D prophylaxis, with routine antenatal anti-D prophylaxis for all and post-delivery prophylaxis guided by cord blood typing. Results show that routine antenatal anti-D prophylaxis and postpartum prophylaxis guided by cord blood typing costs $351 per pregnancy; but that NIPT for fetal RhD status with prophylaxis guided by test results cost $682 per pregnancy.

Teitelbaum et al. (2015) analysed the cost and benefits of NIPT for fetal RhD status in Alberta, Canada. They compared targeted antenatal anti-D prophylaxis based on results of NIPT for RhD status with routine antenatal anti-D prophylaxis for all. Outcomes measured were cost, number of people sensitised and doses of anti-D immunoglobulin administered. Results show that routine prophylaxis for all pregnant people who are RhD negative and not sensitised to RhD antigen costs C$71.43 per pregnancy, but targeted prophylaxis for these pregnant people, based on NIPT test results, costs C$67.20 per pregnancy.

5.2 Modelling possibilities

The model used for the NICE technology appraisal of Routine antenatal anti-D prophylaxis for people who are rhesus D negative (2008; NICE technology appraisal guidance 156) should be used to inform the development of a de novo model. This will ensure consistency between the modelling approaches used in the technology appraisal and the diagnostics assessment of high-throughput NIPT for fetal rhesus D status. This assessment will not update NICE technology appraisal guidance 156.

The preferred timing of NIPT for fetal RhD status may vary in different maternity services to coincide with routine midwifery visits. Different timings of the test should be investigated in the model, using plausible timings informed by specialist advice.

The model should be based on the testing service provided by the International Blood Group Reference Laboratory in Bristol. In the future, other laboratories may set up testing services for high-throughput, NIPT for fetal RhD status. The test accuracy and test costs at these laboratories may differ from the test accuracy and test costs at the International Blood Group Reference Laboratory, Bristol. Sensitivity analyses involving different test accuracy and increased test costs should be included in the economic analysis.

If a RhD negative fetus is identified through high-throughput NIPT, it is anticipated that both routine antenatal anti-D prophylaxis and anti-D immunoglobulin following potentially sensitising events and birth could be avoided by people who are RhD negative and who are not known to be sensitised to the RhD antigen. Alternatively, routine antenatal anti-D prophylaxis could be avoided, but anti-D immunoglobulin following potentially sensitising events and birth could be administered according to current clinical guidelines. The assessment should consider the potential implications of these alternative scenarios and should be investigated in the model if evidence allows.

High-throughput, NIPT for fetal RhD status determination could impact post-delivery testing in one of four ways, which should be investigated in the model:

- Post-delivery cord blood typing and feto-maternal haemorrhage testing would continue to be performed as per current guidelines in all people who are RhD negative, regardless of the fetal RhD status identified through NIPT.
- Post-delivery cord blood typing and feto-maternal haemorrhage testing would be withheld if NIPT of fetal RhD status had identified

a RhD negative fetus, but would continue to be performed in people who are RhD negative if NIPT had identified a RhD positive fetus.

- Post-delivery cord blood typing would be performed if NIPT of fetal RhD status had identified a RhD negative fetus. Feto-maternal haemorrhage testing and post-delivery anti-D immunoglobulin would be administered to people who are RhD negative if NIPT had identified a RhD positive fetus.
- Post-delivery cord blood typing would not be performed in any people who are RhD negative. Feto-maternal haemorrhage testing and post-delivery anti-D immunoglobulin would be administered to people who are RhD negative if NIPT had identified a RhD positive fetus.

6 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Pregnancy is a protected characteristic under the Equality Act 2010. The following potential equality issues have been identified:

- Different RHD genes are found in different ethnic groups. These genetic differences should be considered when interpreting test results to ensure effective use.
- The scope applies equally to pregnant women who are RhD negative and pregnant transgender men who are RhD negative.
- Anti-D immunoglobulin is a blood product, which may not be accepted by people from some religions or cultures. Knowledge of a RhD negative fetus may reduce anxiety in people who do not accept treatment with blood products, but knowledge of a RhD positive fetus may increase anxiety in people who do not accept blood products.

7 Potential implementation issues

7.1 Laboratory capacity

Currently, all high-throughput NIPT for fetal RhD status determination is performed by the International Blood Group Reference Laboratory in Bristol. If all pregnant people in England who are RhD negative were to be tested, this would be approximately 100,000 samples. The International Blood Group Reference Laboratory could scale up capacity in accordance with demand by

employing additional staff and acquiring more analytical platforms. Alternatively, commissioners may wish to explore extending the testing service to other laboratories.

7.2 Sample transport

Samples would need to be transported from local hospital laboratories to the International Blood Group Reference Laboratory in Bristol. The established NHS Blood and Transplant transport system would be used to deliver samples across the country. There would not be a charge for this transport because the transport logistics system is already in place. Cell free fetal DNA is very stable therefore transport is not time critical.

7.3 Procurement

Hospitals will need to budget for the cost of the test. The test may be paid for from the blood and transfusion budget. This is the same budget that funds anti-D immunoglobulin, and therefore costs and savings would be seen in the same area.

7.4 Training

Training would be required for midwives to ensure samples are taken at the appropriate time and sent to the laboratory correctly, and that appropriate action is taken when the result is returned. Training would also be needed for all healthcare professionals who care for people who are RhD negative to ensure they know the correct action if a sensitising event occurs and fetal RhD status is available. It is also important that healthcare professionals know how to interpret and communicate the test results correctly.

7.5 Patient information and consent

Midwives and patient information leaflets can provide information about blood groups, red cell antibodies and high-throughput NIPT for fetal RhD status. The possible consequences and options following test results would also be explained. People who are RhD negative would need to receive this information before they give informed consent to the test and the subsequent management plan. People can still request anti-D immunoglobulin even if the test indicates their fetus is RhD negative.

NIPT of RhD status may also indirectly provide information on the paternity of the fetus.

Appendix A Glossary of terms

ABO typing
A test to determine ABO blood group

Anti-D immunoglobulin
A treatment given to RhD negative pregnant people to prevent sensitisation

Cell-free fetal DNA
Fetal DNA circulating freely in the maternal blood stream

Direct antiglobulin test
Also known as the direct Coombs' test; this test is used to detect antibodies or complement proteins that are bound to the surface of red blood cells

Exchange blood transfusion
A procedure which involves removing aliquots of patient blood and replacing with donor blood in order to remove antibodies and excess bilirubin whilst maintaining adequate circulating blood volume

Feto-maternal haemorrhage
An event which occurs when the membrane barrier between the maternal circulation and fetal circulation ceases to function and fetal cells enter the maternal blood.

Feto-maternal haemorrhage test
Also known as the Kleihauer test; this test is a blood test used to measure the amount of fetal haemoglobin transferred from a fetus to a mother’s blood

Haemolytic disease of the fetus and newborn
A condition where antibodies in a pregnant person’s blood destroy their baby’s blood cells

Jaundice
A condition caused by a build-up of a substance called bilirubin in the blood and body's tissues which results in yellowing of the skin and the whites of the eyes

Phototherapy
Treatment with light which lowers the bilirubin levels in blood through a process called photo-oxidation. The bilirubin is converted into a substance that dissolves easily in water, making it easier for the liver to break down and remove bilirubin.

Potentially sensitising event
An event which may result in fetal cells entering the maternal blood system, for example, during a miscarriage or abortion, having an amniocentesis or chorionic villus sampling, vaginal bleeding or abdominal injury

Prophylaxis
A measure taken to maintain health and prevent disease

RHD pseudogene
A non-functional genomic DNA sequence similar to the RHD gene. The RHD pseudogene is common in RhD negative people of African and Caribbean family origin.

Sensitisation
Sensitisation occurs when cells from a rhesus positive fetus enter the maternal blood system and the mother develops an immune response against the rhesus antigen

Appendix B Abbreviations

CPA	Clinical pathology accreditation
NIPT	Non-invasive prenatal testing
RAADP	Routine antenatal anti-D prophylaxis
RhD	Rhesus D (antigen)
RHD	Rhesus D (gene)

Appendix C Related guidance

Published NICE guidance

Safe midwifery staffing for maternity settings (2015) NICE guideline NG4

Intrapartum care (2014) NICE guideline CG190

Ectopic pregnancy and miscarriage (2012) NICE guideline CG154

Neonatal jaundice (2010) NICE guideline CG98

Routine antenatal anti-D prophylaxis for women who are rhesus D negative (2008) NICE technology appraisal guidance 156

Antenatal care (2008) NICE guideline CG62

Induction of labour (2008) NICE guideline CG70

Postnatal care (2006) NICE guideline CG37

NICE guidance under development

Neonatal jaundice (update SC). NICE guideline (publication expected November 2015)

Preterm labour and birth. NICE guideline (publication expected November 2015)

Intrapartum care for high risk people. NICE guideline (publication expected January 2017)

NICE pathways

The non-invasive prenatal testing for fetal rhesus D status guidance will be included in NICE pathways, for example the antenatal care pathway. It may be appropriate to include the full recommendations of the guidance, or it may only be necessary to give a link to the guidance.

Relevant guidance from other organisations

Qureshi H, Massey E, Kirwan D, et al. (2013) BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. Transfusion Medicine 24 (1): 8-20

The Royal College of Obstetricians and Gynaecologists (2014) The management of women with red cell antibodies during pregnancy. Green-top Guideline No. 65

Scottish National Blood Transfusion Service (2013) Pregnant Women with Red Cell Antibodies: Scottish National Clinical Guidance

Appendix D References

Chitty LS, Finning K, Wade A, et al. (2014) Diagnostic accuracy of routine antenatal determination of fetal RHD status across gestation: population based cohort study. BMJ 4;349:g5243.

Finning K, Martin P, Summers J, et al. (2008) Effect of high throughput RHD typing of fetal DNA in maternal plasma on use of anti-RhD immunoglobulin in RhD negative pregnant women: prospective feasibility study BMJ 12; 336 (7648): 816-8.

Hawk AF, Chang EY, Shields SM, et al. (2013) Costs and clinical outcomes of noninvasive fetal RhD typing for targeted prophylaxis. Obstetrics and Gynecology 122(3): 579-585.

National Comparative Audit of Blood Transfusion 2013 Audit of the use of Anti-D Immunoglobulin Prophylaxis

NHS Choices Rhesus disease available from http://www.nhs.uk/Conditions/Rhesus-disease/Pages/Introduction.aspx

Oxenford K, Silcock C, Hill M, et al. (2013) Routine testing of fetal Rhesus D status in Rhesus D negative women using cell-free fetal DNA: an investigation into the preferences and information needs of women. Prenatal Diagnosis 33(7): 688-94.

Patient Haemolytic Disease of the Newborn available from http://patient.info/doctor/haemolytic-disease-of-the-newborn

Soothill PW, Finning K, Latham T, et al. (2014) Use of cffDNA to avoid administration of anti-D to pregnant women when the fetus is RhD-negative: implementation in the NHS. BJOG

Szczepura, A., Osipenko, L., and Freeman, K. (2011) A new fetal RHD genotyping test: costs and benefits of mass testing to target antenatal anti-D prophylaxis in England and Wales. BMC Pregnancy and Childbirth 11: 5.

Teitelbaum L, Metcalfe A, Clarke G, et al. (2015) Costs and benefits of non-invasive fetal RhD determination. Ultrasound in Obstetrics and Gynecology 45(1): 84-88.