NICE National Institute for Health and Care Excellence

NICE guidance

High-throughput non-invasive prenatal testing for fetal RHD genotype

Diagnostics guidance

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 High-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* genotype is recommended as a cost-effective option to guide antenatal prophylaxis with anti-D immunoglobulin, provided that the overall cost of testing is £24 or less. This will help reduce unnecessary use of a blood product in pregnant women, and conserve supplies by only using anti-D immunoglobulin for those who need it.

1.2 Cost savings associated with high-throughput NIPT for fetal *RHD* genotype are sensitive to the unit cost of the test, additional pathway costs and implementation costs. Trusts adopting NIPT should collect and monitor the costs and resource use associated with implementing testing to ensure that cost savings are achieved (see section 6.1).

2 Clinical need and practice

The problem addressed

2.1 NICE technology appraisal guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative recommends anti-D immunoglobulin for all rhesus-D (D) negative pregnant women who are not known to be sensitised to the D antigen, to reduce the risk of sensitisation. The British Committee for Standards in Haematology (BCSH) guideline on anti-D immunoglobulin to prevent haemolytic disease of the fetus and newborn also recommends that all D-negative pregnant women who are not known to be sensitised to D antigen have anti-D immunoglobulin after:

- potentially sensitising events
- birth, if the baby is confirmed to be D positive by cord blood typing.

2.2 Anti-D immunoglobulin is produced from the pooled plasma donated by large numbers of D-negative people who have had a transfusion of D-positive red cells to stimulate the production of D antibodies. It is a finite resource and, because there have been shortages in the past, it needs to be used carefully to maintain stocks. Anti-D immunoglobulin is a blood product and may also carry the risks common to all blood products, including physiological reactions, processing errors and the potential future risk of unknown blood-borne viruses or prion diseases. Physiological reactions must be reported to the Medicines and Healthcare products Regulatory Agency and processing errors to the Serious Hazards of Transfusion Scheme.

2.3 High-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* genotype involves analysing cell-free fetal DNA in maternal blood and is intended for use in pregnant women who are D negative and are not sensitised to D antigen. It is a laboratory-developed test offered by the International Blood Group Reference Laboratory, Bristol. This laboratory is an accredited NHS Blood and Transplant Laboratory that is currently

providing NIPT for *RHD* genotype for some NHS patients.

2.4 High-throughput NIPT for fetal *RHD* genotype would allow D-negative women who are carrying a D-negative fetus to avoid unnecessary treatment with anti-D immunoglobulin.

2.5 High-throughput NIPT for fetal *RHD* genotype would allow D-negative women to make an informed choice about whether to have treatment with anti-D immunoglobulin. This may improve adherence to anti-D immunoglobulin treatment, reduce the number of sensitisations and so reduce haemolytic disease of the fetus and newborn in later pregnancies.

The condition

2.6 During pregnancy, small amounts of fetal blood can enter the maternal circulation (an event called fetomaternal haemorrhage). The presence of fetal D-positive cells in the maternal circulation, after fetomaternal haemorrhage, can cause a mother who is D negative to produce antibodies against the D antigen on the fetal blood cells (anti-D) – a process called sensitisation. Sensitisation can happen at any time during pregnancy, but is most common during the third trimester and delivery. It can follow events in pregnancy known to be associated with fetomaternal haemorrhage, such as medical interventions, terminations, late miscarriages, antepartum haemorrhage and abdominal trauma. These are called potentially sensitising events.

2.7 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 D antigen from a D-positive fetus during a later pregnancy, the immune response is quicker and much greater. The anti-D produced by the mother can cross the placenta and cause haemolytic disease of the fetus and newborn. This can cause severe fetal anaemia, leading to fetal heart failure, fluid retention and swelling (hydrops), and intrauterine death.

2.8 The risk of sensitisation can be reduced if D-negative pregnant women have anti-D immunoglobulin. Before anti-D immunoglobulin was available,

the incidence of sensitisation in D-negative women after the birth of 2 D-positive babies was about 16%. Haemolytic disease of the fetus and newborn, which occurred in about 1% of all births, was a significant cause of morbidity and mortality. After routine postpartum anti-D prophylaxis was introduced, the incidence of D sensitisation dropped to about 2%. The sensitisation rate has further reduced since the introduction of routine antenatal anti-D prophylaxis.

2.9 In England, there were 646,904 births from April 2013 to March 2014, of which about 15% (97,036 births) were to D-negative women. About 40% of these women carry a D-negative fetus (around 39,000 per year) and so do not need to have anti-D immunoglobulin. D-negative status occurs in about 15% of people of white European family origin, about 3% to 5% of people of black African family origin, and is very rare in people of eastern Asian origin. Most D-negative people of white European family origin have an *RHD* gene deletion; less than 1% have *RHD* gene variants. However, in D-negative people of black African family origin, 66% have an inactive *RHD* gene (the *RHD* pseudogene), which mostly results from genes that contain D sequences but do not produce D antigen.

The diagnostic and care pathways

Care for D-negative pregnant women who are not sensitised to D antigen

2.10 In current practice, babies born to women who are D negative and not sensitised to D antigen have their Rh blood group determined after birth, using cord blood typing. Testing to find out the *RHD* genotype of the fetus during pregnancy is not currently done in most centres in the NHS.

2.11 The NICE guideline on antenatal care and the BCSH guideline on blood grouping and antibody testing in pregnancy recommend that women should be offered testing for ABO and Rh blood group in early pregnancy. All women identified as D-negative would be tested for the presence of D antibodies, regardless of whether they are known to be sensitised or not. To prevent sensitisation in women identified as D-negative but without D antibodies, anti-D immunoglobulin is recommended, both as

prophylaxis and after potentially sensitising events.

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

2.13 The guideline from the BCSH on using anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn recommends that all D-negative pregnant women, who are not known to be sensitised to D antigen, have anti-D immunoglobulin after:

- potentially sensitising events
- birth, if the baby is confirmed to be D positive by cord blood typing.

The BCSH guideline also states that RAADP should be given regardless of, and in addition to, any anti-D immunoglobulin that may have been given for a potentially sensitising event.

Care for D-negative pregnant women who are sensitised to D antigen

2.14 The Royal College of Obstetricians and Gynaecologists' (RCOG) guidance on managing women with red cell antibodies during pregnancy recommends that all women who are D negative and are sensitised to D antigen should:

- attend pre-pregnancy counselling with a clinician who has knowledge and expertise in managing 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 anti-D is present.

  The NIPT offered to D-negative women who are sensitised to D antigen is different to the high-throughput NIPT for fetal *RHD* genotype assessed in this diagnostics guidance, and has different diagnostic accuracy.

2.15 The RCOG guideline and the BCSH guideline on blood grouping and antibody testing in pregnancy also recommend that if a D-positive fetus is identified, additional monitoring and treatment are needed during the pregnancy, which should include:

- measuring D-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 D-antibody levels are rising or are at a level above a specific threshold, or ultrasound features suggest fetal anaemia
- weekly monitoring by ultrasound if D-antibody levels rise above a specific threshold
- fetal blood sampling if ultrasound shows signs of fetal anaemia, and considering intrauterine transfusion
- considering early delivery of the baby, depending on antibody levels and whether any fetal therapy has been needed
- using continuous electronic fetal heart monitoring during labour.

2.16 After the baby is born, the RCOG guideline recommends that assessments should include:

- a direct antiglobulin test to detect maternal antibodies adhering to the baby's red blood cells
- confirmation of the baby's blood group (using a cord blood sample)
- haemoglobin level measurement to test for anaemia
- bilirubin level measurement to test for jaundice

- clinical assessment of the baby's neurobehavioural state and observations for jaundice and anaemia.

2.17 The NICE guideline on jaundice in newborn babies under 28 days gives recommendations on diagnosing and treating jaundice.

3 The diagnostic tests

The assessment compared 1 intervention test with 1 comparator test.

The intervention

3.1 High-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* genotype is a laboratory developed test offered by the International Blood Group Reference Laboratory, Bristol (NHS Blood and Transplant). The test uses a real-time quantitative polymerase chain reaction (PCR) method for identifying fetal *RHD* genotype from fetal DNA in the plasma of rhesus-D (D) negative women. The test analyses cell-free fetal DNA, in the form of small fragments of fetal extracellular DNA shed from the placenta and circulating freely in the maternal plasma. The level of cell-free fetal DNA in maternal blood increases throughout the pregnancy and rapidly falls after delivery. Most women who are D negative do not have copies of the *RHD* gene; therefore, the presence of the *RHD* gene in a D-negative pregnant woman suggests a D-positive fetus.

3.2 High-throughput NIPT is carried out using 4 ml to 6 ml of maternal anti-coagulated blood. DNA extraction is done using an automated robotic platform (MDx BioRobot, Qiagen), which can rapidly process samples. The robotic platform is also used as a liquid handler to dispense samples and reagents. PCR is then done 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. The samples can be 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.

3.3 The exon 5 assay amplifies the *RHD* gene, whereas the exon 7 assay amplifies both the *RHD* gene and the *RHD* pseudogene. A threshold value of less than 42 cycles is interpreted as a positive signal and an algorithm is used to determine the fetal *RHD* genotype. Results are reported as 'D-positive', 'D-negative' or 'indeterminate – treat as

D-positive'. The result would influence whether to offer routine antenatal anti-D prophylaxis and anti-D immunoglobulin to D-negative women, who are not sensitised to D antigen, after potentially sensitising events.

The comparator

3.4 The comparator in the assessment was cord blood typing, which is used to determine the Rh blood group of a baby after birth.

4 Evidence

The diagnostics advisory committee (section 8) considered evidence on high-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* genotype from several sources (section 9). Full details of all the evidence are in the committee papers.

Clinical effectiveness

Assessment of test accuracy

4.1 Eight studies reported the diagnostic accuracy of high-throughput NIPT for fetal *RHD* genotype, all of which were prospective studies carried out in European countries. Four studies were done in England, 3 of which were based in Bristol. Cord blood typing was the reference standard in all studies. Six studies were considered to be at low risk of bias and 2 studies (Akolekar et al. 2011; Thurik et al. 2015) were judged to be at high risk of bias. Except for 2 studies (Akolekar et al. 2001; Wikman et al. 2012), the results of the studies were considered broadly applicable to using high-throughput NIPT for fetal *RHD* genotype for nationwide testing in the UK.

4.2 It is expected that, in the UK, women with inconclusive NIPT results will be treated as having a positive test with no further testing. Data on inconclusive results were not reported in 2 studies (Thurik et al. 2015; Grande et al. 2013). So, 4 approaches to the diagnostic accuracy analysis were considered:

- women with inconclusive tests were treated as test positive (including Thurik et al. 2015 and Grande et al. 2013)
- women with inconclusive tests were treated as test positive (excluding Thurik et al. 2015 and Grande et al. 2013)
- excluding all women with inconclusive test results
- including only studies done in Bristol.

4.3 Results of the hierarchical bivariate meta-analyses are shown in table 1. In all analyses, women in whom NIPT was carried out at or before 11 weeks' gestation were excluded because the test is known to be less accurate before 11 weeks. NIPT for fetal *RHD* genotype is very accurate among women with a rhesus-D (D) positive fetus; only 2 to 4 in 1,000 such women will have a negative test result and so be at risk of sensitisation because they would not be offered antenatal anti-D immunoglobulin. NIPT for fetal *RHD* genotype is slightly less accurate among women with a D-negative fetus; between 13 and 57 in 1,000 such women will have a positive test result and so be offered antenatal anti-D immunoglobulin unnecessarily.

Table 1 Meta-analysis results

Analysis case	Number of studies	False-negative rate (at risk of sensitisation) estimate (% [95% CI])	False-positive rate (unnecessary anti D) estimate (% [95% CI])
Inconclusive treated as test positive (including Thurik et al. and Grande et al.)	8	0.34 (0.15–0.76)	3.86 (2.54–5.82)
Inconclusive treated as test positive (excluding Thurik et al. and Grande et al.)	6	0.38 (0.15–0.94)	4.37 (2.79–6.78)
Excluding all inconclusive test results	8	0.35 (0.15–0.82)	1.26 (0.87–1.83)
Studies only done in Bristol	3	0.21 (0.09–0.48)	5.73 (4.58–7.16)

Abbreviation: CI, confidence interval.

4.4 The analysis of the 3 Bristol studies gave a slightly lower false-negative rate (0.21%; 95% confidence interval [CI] 0.09 to 0.48) and a higher false-positive rate (5.73%; 95% CI 4.58 to 7.16) than analyses including other studies. This suggests that the Bristol high-throughput NIPT approach may use a different test threshold compared with the testing done in other studies; minimising false-negative findings, with a

consequent increase in the false-positive rate.

4.5 There was considerable variation in rates of inconclusive tests across studies, ranging from 0.4% to 14.3%. The most likely causes for this variability are differences in how the NIPT was done (such as different numbers and types of exons considered) and differences in characteristics of study populations (for example, different proportions of women of black African family origin). Based on a meta-analysis, the average rate of inconclusive test results was estimated to be 4.0% (95% CI 1.5 to 10.3) if all studies reporting inconclusive results were included, and 6.7% (95% CI 3.7 to 11.7) if only the Bristol studies were included.

4.6 An analysis of the effect of the timing of high-throughput NIPT for fetal *RHD* genotype on diagnostic accuracy suggested that false-negative rates were higher before 11 weeks' gestation, and thereafter false-negative rates were consistent, irrespective of timing. The effect of the timing of high-throughput NIPT on the number of inconclusive test results suggested that the percentage of inconclusive results drops as the gestational age increases from 11 weeks.

Assessment of clinical outcomes

4.7 Seven studies reported the clinical effectiveness of NIPT for fetal *RHD* genotype, all of which were observational and carried out in European countries. The sample size of the studies ranged from 284 to 15,126 and most participants were of white European family origin. Only 2 studies compared women having NIPT for fetal *RHD* genotype with controls (Tiblad et al. 2013; Banch Clausen et al. 2014). Tiblad et al. (2013) was considered to be at serious risk of bias, and Banch Clausen et al. (2014) was considered to be at critical risk of bias. The generalisability of these 2 studies to NHS clinical practice was limited because participants in the control group did not have routine antenatal anti-D prophylaxis (RAADP). The other 5 studies only reported non-comparative-effectiveness data for women having NIPT for fetal *RHD* genotype. Data from these studies were supplemented with data from a UK audit on anti-D immunoglobulin use (National comparative audit of blood transfusion: 2013 audit of anti-D immunoglobulin prophylaxis) for a comparison with current practice.

4.8 Tiblad et al. (2013) compared targeted RAADP in the first trimester with routine care (postpartum anti-D prophylaxis only) in Sweden. They reported the incidence of D sensitisation in the cohort that had high-throughput NIPT for fetal *RHD* genotype as 0.26% (95% CI 0.15 to 0.36%; n=8347) compared with 0.46% (95% CI 0.37 to 0.56%; n=18,546) in the historical control cohort. High-throughput NIPT for fetal *RHD* genotype was associated with a significant risk reduction in sensitisation (unadjusted risk ratio [RR] 0.55; 95% CI 0.35 to 0.87) compared with historical controls. An updated analysis reported in a linked conference abstract (Neovius et al. 2015) found an adjusted odds ratio of 0.41 (95% CI 0.22 to 0.87).

4.9 Seven studies reported uptake rates of NIPT for fetal *RHD* genotype. Uptake rates ranged from 70% to more than 95% across the studies. In a pilot study done by Soothill et al. (2015) in 3 maternity services in the south-west of England, only 70% of eligible women joined the study in the first 6 months. The larger English study done by Chitty et al. (2014) reported that 88% of the 3,069 participants consented to have NIPT for fetal *RHD* genotype. The only country that reported nationwide uptake data was the Netherlands, where more than 95% of eligible women had NIPT for fetal *RHD* genotype. The studies generally noted that uptake is likely to increase over time if a nationwide screening programme is implemented.

4.10 The uptake of RAADP in women who accepted NIPT and had a positive result was reported in 4 studies and ranged from 86.0% to 96.1%. Of the larger studies, Van der Ploeg et al. (2015) reported nationwide data on women having NIPT for fetal *RHD* genotype in the Netherlands, where 96.1% of about 18,383 women with a positive test result had RAADP. Tiblad et al. (2013) reported a slightly lower rate, with 90% of 5,104 women with a positive NIPT result having RAADP. Data on the uptake of RAADP in women who had a negative test result, those who had an inconclusive test result, and those who refused NIPT for fetal *RHD* genotype, were limited. None of the studies reported whether all the women who had RAADP had the intended dosage at the intended time, or what proportion of women had additional anti-D immunoglobulin because of a potentially sensitising event.

4.11 The uptake of postpartum anti-D prophylaxis in women who accepted NIPT for fetal *RHD* genotype and had a positive test result was reported in 3 studies. Van der Ploeg et al. (2015) reported nationwide data on women having NIPT for fetal *RHD* genotype in the Netherlands, where 92% of about 18,383 women had postpartum anti-D prophylaxis. A subgroup analysis by Banch Clausen et al. (2014) found slightly higher uptake of postpartum anti-D prophylaxis among women who had NIPT (99.7%, 353/354) compared with those who did not have NIPT (95.7%, 66/69). Damkjaer et al. (2012) reported a similar rate among women who had NIPT (99.3%, 151/152). None of the included studies reported whether all women who had postpartum anti-D prophylaxis had the intended dosage at the intended time.

4.12 Outcome measures relating to anti-D immunoglobulin administration were reported in 3 non-comparative studies. Soothill et al. (2015) reported a significant 6% reduction per month in anti-D immunoglobulin administration (95% CI 4 to 8) over a 6-month period in 3 maternity services in the south west of England. The total use of anti-D immunoglobulin fell by about 29%, corresponding to 35% of D-negative women not having anti-D immunoglobulin in their pregnancy unnecessarily. Similar results were also seen by Banch Clausen et al. (2014), who reported that 37.1% of women avoided unnecessary anti-D immunoglobulin within 2 years of the introduction of a programme of NIPT for fetal *RHD* genotype. Grande et al. (2013) reported that, of 95 women carrying a D-negative fetus, 5 women requested anti-D immunoglobulin; so, unnecessary anti-D immunoglobulin was avoided in 95% of women carrying a D-negative fetus.

4.13 To better understand the likely consequences of implementing NIPT for fetal *RHD* genotype and basing antenatal anti-D immunoglobulin administration on its results, the external assessment group did a simulation study. The following assumptions were made:

- When needed, antenatal anti-D immunoglobulin is offered at around 28 weeks.
- Postpartum anti-D prophylaxis is offered based on the result of cord blood typing.
- Cord blood typing is 100% accurate.

- There are no adverse consequences of giving anti-D immunoglobulin.

4.14 The results of the simulation study, summarised in table 2, showed that using NIPT for fetal *RHD* genotype leads to a substantial reduction in RAADP use, from 99% of D-negative women to 65.9%. This decline is similar in size to that seen by Soothill et al. (2015). The decrease is because of the drop (from 39% to 5.7%) in women with D-negative fetuses needlessly having anti-D immunoglobulin. Using NIPT for fetal *RHD* genotype means that about 1.2% of women miss having possibly beneficial RAADP, compared with 0.6% when using a universal RAADP approach with no testing.

Table 2a Results of the simulation study: antenatal anti D prophylaxis

Outcome	Treatment approach	Proportion of women
Antenatal anti-D given	Universal anti-D	99.0%
Antenatal anti-D given	Based on NIPT	65.9%
Unnecessary anti-D given (D-negative fetus)	Universal anti-D	38.9%
Unnecessary anti-D given (D-negative fetus)	Based on NIPT	5.7%
Anti-D not given (D-positive fetus)	Universal anti-D	0.6%
Anti-D not given (D-positive fetus)	Based on NIPT	1.2%

Table 2b Results of the simulation study: sensitised during pregnancy

Treatment approach	Proportion of women
Postpartum and emergency anti-D only	0.641%
Universal anti-D	0.281%
Based on NIPT with postpartum anti-D	0.284%
Based on NIPT with no postpartum anti-D for women who test negative	0.294%

Table 2c Results of the simulation study: deaths because of sensitisations

Treatment approach	Proportion of women
Postpartum and emergency anti-D only	0.0198%
Universal anti-D	0.0086%
Based on NIPT with postpartum anti-D based on cord blood typing	0.0091%
Based on NIPT with no postpartum anti-D for women testing negative	0.0091%

Abbreviation: NIPT, non invasive prenatal testing.

4.15 Assuming all women still have postpartum cord blood typing and postpartum anti-D prophylaxis if needed, the simulation study showed that NIPT would result in about 3 extra sensitisations per 100,000 women. If cord blood typing is not done, there would be about 13 extra sensitisations per 100,000 women. These increases are small compared with the total number of sensitisations because of anti-D immunoglobulin failure and non-adherence to anti-D immunoglobulin treatment (around 281 per 100,000 women), and compared with not using RAADP at all (around 641 per 100,000).

4.16 Results of the simulation study also showed that using NIPT for fetal *RHD* genotype is unlikely to have any meaningful effect on mortality in later pregnancies; if women with a negative NIPT result never have postpartum anti-D prophylaxis, there would be about 5 extra fetal or neonatal deaths per 1 million D-negative women. In current practice, there are an estimated 86 fetal or neonatal deaths per 1 million D-negative women.

Assessment of implementation issues

4.17 Twelve studies were identified in a review of implementation of NIPT for fetal *RHD* genotype. Most studies reported that NIPT for fetal *RHD* genotype was feasible. Several studies reported potential issues relating to implementation, such as adherence to the anti-D prophylaxis

programme. Some studies highlighted the importance of short transport times for samples and effective management of transporting samples. The need for greater awareness of NIPT among physicians and midwives was also identified in some studies.

4.18 A UK-based survey (Oxenford et al. 2013) showed that, although most of the women surveyed supported the implementation of NIPT, their current knowledge of Rh blood groups and anti-D treatment was limited, which could be a barrier to implementation.

Cost effectiveness

Review of economic evidence

4.19 Seven studies were identified in a review of existing studies on the cost effectiveness of high-throughput NIPT to determine fetal *RHD* genotype in pregnant women who are D negative and are not sensitised to the D antigen. The quality of the included studies' findings was uncertain because they did not report the validity of the diagnostic accuracy outcomes used. The degree of uncertainty in the cost-effectiveness estimates was also difficult to establish.

4.20 Results across the existing economic studies were conflicting. Only 1 study found NIPT for targeting RAADP to be cost saving compared with non-targeted RAADP. Two studies reported that NIPT for fetal *RHD* genotype was cost saving compared with no RAADP, that is, compared with postpartum anti-D prophylaxis only. Three studies reported that NIPT for fetal *RHD* genotype was not cost effective or was of no economic benefit. Only 1 study directly related to the UK (Szczepura et al. 2011).

Modelling approach

4.21 The external assessment group developed a de novo economic model designed to assess the cost effectiveness of high-throughput NIPT to determine fetal *RHD* genotype in pregnant women who are D negative and are not sensitised to D antigen.

Model structure

4.22 A decision tree cohort approach was developed to estimate the costs and health outcomes with and without high-throughput NIPT for fetal *RHD* genotype. The treatment part of the model was based closely on the economic model used in the NICE technology appraisal guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative, developed by researchers at the School of Health and Related Research (ScHARR).

4.23 In the model, a pregnant woman enters after being identified as D negative and not sensitised to D antigen, based on testing at first contact with the doctor or midwife, or at the booking appointment (at 8 to 12 weeks' gestation). The first part of the model divides the cohort according to fetal *RHD* genotype and treatment. This determines when having RAADP is appropriate, inappropriate, or unnecessary, and when avoidance of RAADP is potentially harmful. Test performance, adherence to high-throughput NIPT for fetal *RHD* genotype and RAADP, and the effectiveness of RAADP all inform the estimation of the probability of sensitisation. The second part of the model considers the short- and long-term consequences of sensitisations, such as fetal or neonatal death, and minor or major fetal development problems in later pregnancies.

4.24 Four alternative ways (see table 3) that using high-throughput NIPT may affect the existing postpartum care pathway were considered:

- Postpartum scenario 1 (PP1): postpartum cord blood typing and fetomaternal haemorrhage testing would continue to be done, based on current guidelines, in all women regardless of the fetal *RHD* genotype identified with high-throughput NIPT.
- Postpartum scenario 2 (PP2): postpartum cord blood typing and fetomaternal haemorrhage testing (and by implication anti-D immunoglobulin) would be withheld if high-throughput NIPT for fetal *RHD* genotype identified a D-negative fetus, but would continue to be done if high-throughput NIPT was inconclusive or had identified a D-positive fetus.

- Postpartum scenario 3 (PP3): postpartum cord blood typing would be done if high-throughput NIPT for fetal *RHD* genotype identified a D-negative fetus. Fetomaternal haemorrhage testing and post-delivery anti-D immunoglobulin would be provided if high-throughput NIPT was inconclusive or identified a D-positive fetus.
- Postpartum scenario 4 (PP4): postpartum cord blood typing would not be carried out in any women. Fetomaternal haemorrhage testing and post-delivery anti-D immunoglobulin would be provided if high-throughput NIPT was inconclusive or had identified a D-positive fetus.

Table 3 Characteristics of the postpartum strategies

Scenario	High-throughput NIPT result	Cord blood typing	FMH testing	Postpartum anti-D
Postpartum scenario 1	Any	Yes	Yes if CBT+	As guided by CBT and FMH testing
Postpartum scenario 2	Negative	No	No	No
Postpartum scenario 2	Positive or inconclusive	Yes	Yes if CBT+	As guided by CBT and FMH testing
Postpartum scenario 3	Negative	Yes	Yes if CBT+	As guided by CBT and FMH testing
Postpartum scenario 3	Positive or inconclusive	No	Yes	Yes with additional dose per FMH test
Postpartum scenario 4	Negative	No	No	No
Postpartum scenario 4	Positive or inconclusive	No	Yes	Yes with additional dose per FMH test

Abbreviations: CBT, cord blood typing; NIPT, non invasive prenatal testing; FMH, fetomaternal haemorrhage; +, positive.

Model inputs

4.25 The annual number of pregnancies in D-negative women in England was

estimated to be 99,225. This represents a cross section of all pregnancies, and the proportions of first, second, third and later pregnancies are used to characterise the total fertility rate of a typical D-negative woman. This estimate was based on a birth rate of 12.2 per 1,000 women per year and assumes that 15% of the population is D negative. The proportion of D-positive babies born to women who are D negative was estimated as 61.6%. This rate was applied across all pregnancies, that is, the first and later pregnancies.

4.26 The diagnostic accuracy of high-throughput NIPT for fetal *RHD* genotype and the proportion of inconclusive results were based on the meta-analyses done in the clinical-effectiveness assessment. The base case used the pooled results for the subgroup of UK (Bristol-based) studies in which inconclusive results were considered as test positive. These studies were considered the most relevant to NHS clinical practice. Sensitivity was 0.998 (95% CI 0.992 to 0.999), specificity was 0.942 (95% CI 0.920 to 0.959) and the rate of inconclusive results was 6.7%.

4.27 For consistency, this diagnostics assessment used the clinical effectiveness of RAADP that was established in the NICE technology appraisal guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative. Evidence for the clinical effectiveness of postpartum anti-D prophylaxis was taken from a Cochrane review (Crowther et al. 1997). The clinical-effectiveness estimates are presented in table 4.

Table 4 Clinical effectiveness of RAADP and postpartum anti-D prophylaxis

Outcome	NICE guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative	Crowther et al. (1997; sensitisation 6 months after delivery)
Odds ratio: sensitisation with RAADP (compared with no RAADP, conditional on having postpartum anti-D prophylaxis) (95% CI)	0.37 (0.21 to 0.65)	-

Outcome	NICE guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative	Crowther et al. (1997; sensitisation 6 months after delivery)
Odds ratio: sensitisation at birth, follow-up up to 6 months, with postpartum anti-D prophylaxis (compared with no postpartum anti-D prophylaxis, conditional on no RAADP) (95% CI)	-	0.08 (0.06 to 0.11)
Sensitisation rate without RAADP (conditional on having postpartum anti-D prophylaxis) (95% CI)	0.95 (0.18 to 1.71)	0.95 (0.18 to 1.71) Baseline sensitisation rate of no RAADP assumed the same
Sensitisation rate with RAADP (95% CI)	0.35 (0.29 to 0.40)	-
Sensitisation rate without RAADP and without postpartum anti-D prophylaxis (95% CI)	-	10.7 (8.0 to 13.8)

Abbreviations: CI, confidence interval; RAADP, routine antenatal anti-D prophylaxis.

4.28 The number of potentially sensitising events was taken from the recent UK audit on anti-D immunoglobulin use (National comparative audit of blood transfusion: 2013 audit of anti-D immunoglobulin prophylaxis). The probability of women having at least 1 (reported) potentially sensitising event was estimated as 15.5%. Of these, 69.3% were estimated to have had a fetomaternal haemorrhage test and 95.8% were estimated to have had anti-D immunoglobulin after the event. It was estimated that about 80% of these events happened after 20 weeks' gestation, and it was assumed that these events were treated with the minimum required dose of 500 IU anti-D immunoglobulin. For the remaining 20% of events (before 20 weeks' gestation), it was assumed that women had the minimum required dose of 250 IU anti-D immunoglobulin.

4.29 The National comparative audit of blood transfusion: 2013 audit of anti-D immunoglobulin prophylaxis was used to provide estimates of adherence to RAADP. It reported that, out of all eligible women: 99% had at least 1 RAADP injection; full adherence (that is the correct dose at the correct time) was better with the single-dose regimen (90%) compared with the 2-dose regimen (59%); 98.4% had postpartum anti-D prophylaxis; and 96% had anti-D immunoglobulin for documented potentially sensitising events. Within the economic model, it was assumed that adherence to RAADP was 99.0% and that adherence to postpartum anti-D prophylaxis was 98.4%. There was limited evidence on adherence to NIPT for fetal *RHD* genotype, so it was assumed that using NIPT has no additional effect on adherence to anti-D prophylaxis.

4.30 The effects of sensitisation on later pregnancies were taken from Finning et al. (2008) and the NICE technology appraisal guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative. The proportion of fetal or neonatal deaths was estimated to be 5%; and the proportion of babies affected with minor or major developmental problems was estimated to be 6% or 5% respectively. Minor developmental problems were estimated to last 16 years and the life expectancy for a person with major developmental problems was estimated to be 59.5 years.

Costs

4.31 The estimated cost of high-throughput NIPT for fetal *RHD* genotype included consumables, staffing, equipment, and indirect and overhead costs. The estimated cost was based on testing at full capacity, that is, dealing with at least 100,000 samples per year. The unit cost per sample may vary, because it is a function of capacity and the annual predicted level of usage of each testing machine. Also, a royalty fee is under negotiation and will need to be added to the cost of the test. The cost of high-throughput NIPT for fetal *RHD* genotype remains commercial in confidence at the time of writing this diagnostics guidance.

4.32 The cost of anti-D immunoglobulin was taken from the British national formulary. Currently 2 brands (D-Gam and Rhophylac) and 4 doses (250-, 500-, 1,500- and 2,500-unit vials) are available. Weighted

averages based on recommended dose regimens and market share were calculated. The estimated costs were: £31.69 for anti-D immunoglobulin for potentially sensitising events; £41.58 for RAADP; and £35.69 for postpartum anti-D prophylaxis. The cost of giving anti-D immunoglobulin was set to £5.

4.33 In current practice, cord blood typing is done to confirm the baby's Rh blood group, and maternal blood samples are tested for fetomaternal haemorrhage after birth. The costs, updated to 2015 prices, for cord blood typing (£4.18) and associated phlebotomy (£3.32) were taken from Szczepura et al. (2011). The cost of fetomaternal haemorrhage testing by flow cytometry was estimated to be £128.10.

4.34 The relevant interventions for maternal and neonatal sensitisation were taken from the NICE technology appraisal guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative. Unit costs were taken from the NHS reference costs 2014/15. This resulted in an estimated average total cost per sensitisation of £3,167. The estimated annual costs for minor (£111) and major (£574) development problems were also assumed to be the same as in the NICE technology appraisal guidance (updated to 2015 prices).

Health-related quality of life

4.35 The following utilities were assumed in the model: minor developmental problems, 0.85; major developmental problems, 0.42; and general population, 0.88. These values are the same as those used in the NICE technology appraisal guidance on routine antenatal anti-D prophylaxis for women who are rhesus negative.

Base-case results

4.36 Key assumptions made in the model were:

- Sensitisations do not affect the pregnancy in which they occur.
- Anti-D immunoglobulin used within 1 pregnancy has no effect in reducing sensitisations during the next pregnancy.

- The proportion of D-negative women is based on estimates from people of white European family origin.
- The proportion of D-positive babies born to D-negative women is assumed to be the same irrespective of pregnancy number.
- The number of D-positive babies in the model is determined by combining the probability, in the general population of D-negative women, of having a D-positive baby (61.6%) with the sensitivity and specificity of NIPT (in which inconclusive results are treated as test positive).
- The probability of having a D-positive baby in women with inconclusive test results is based on the pooled probability in the study populations used to inform the diagnostic accuracy estimate.
- All NIPT is assumed to be done early enough to determine the need for RAADP at 28 weeks' gestation.
- RAADP is only offered to women in whom the NIPT result indicates that their fetus is D positive or in whom the results are inconclusive.
- Women with an inconclusive NIPT result are treated the same as women who test positive in terms of RAADP, and tests and treatment after potentially sensitising events.
- Women offered RAADP will also be offered supplementary anti-D immunoglobulin at the minimum dose needed for any potentially sensitising events.
- Potentially sensitising events that involve fetal death are assumed to be independent of previous sensitisation within the same pregnancy.
- Women with false-negative test results indicated by cord blood typing and who have postpartum anti-D prophylaxis are assumed to have a sensitisation rate of 0.95%.
- Adherence to RAADP is assumed to be the same with and without NIPT; similarly, adherence to postpartum anti-D prophylaxis is assumed to be the same with or without NIPT.
- There are no adverse health effects from using anti-D immunoglobulin.

4.37 Results show that all NIPT strategies cost less, but are less effective than the comparator, current clinical practice (table 5). Strategies PP1 and PP3 are associated with smaller quality-adjusted life year (QALY) losses than PP2 and PP4. This is because in both PP1 and PP3, cord blood typing is used to identify false-negative results, which would allow women who had been incorrectly identified as having a D-negative baby, and so had not been offered RAADP, to have postpartum anti-D prophylaxis. This would reduce the number of sensitisations, therefore reducing QALY losses.

Table 5 Base-case results (costs and QALYs presented are per 100,000 pregnancies)

Strategies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ saved/ QALY lost)
No test and RAADP (current practice)	£15,983,725	2,433,756	N/A	N/A	N/A
Postpartum scenario 1 versus no test and RAADP	£15,400,187	2,433,756	−£583,538	−0.46	£1,269,050
Postpartum scenario 2 versus no test and RAADP	£15,312,630	2,433,737	−£671,095	−19.13	£35,087
Postpartum scenario 3 versus no test and RAADP	£15,498,942	2,433,756	−£484,783	−0.46	£1,054,281
Postpartum scenario 4 versus no test and RAADP	£15,410,610	2,433,737	−£573,114	−19.13	£29,964

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RAADP, routine antenatal anti D prophylaxis.

4.38 The variations in costs between the 4 strategies were mainly driven by different postpartum testing costs and postpartum anti-D prophylaxis costs. The added cost of managing sensitisations and their associated

health consequences in later pregnancies was largest for the strategies with more sensitisations (PP2 and PP4), and was very small for strategies PP1 and PP3.

4.39 In the fully incremental analysis of NIPT for fetal *RHD* genotype for the different postpartum testing strategies, PP3 and PP4 were dominated. Strategy PP4 was dominated by strategy PP2 because it had the same number of QALYs but was more expensive than PP2. Strategy PP3 was dominated by strategy PP1 because it had the same number of QALYs but was more expensive than PP1.

4.40 The cost-effectiveness acceptability curve showed that PP1 had the highest probability of being cost effective, with 0.65 and 0.73 for maximum acceptable incremental cost-effectiveness ratio (ICER) values of £20,000 and £30,000 per QALY gained respectively. For the same maximum acceptable ICER values, the probability of PP2 being cost effective was 0.30 and 0.22 respectively.

Sensitivity and scenario analyses

4.41 Sensitivity analyses showed that the results of the economic model are robust to small changes in the clinical effectiveness of RAADP, the timing of testing (between 11 and 23 weeks) and adherence to anti-D immunoglobulin treatment.

4.42 A sensitivity analysis was done on the diagnostic accuracy of NIPT. When the diagnostic accuracy of NIPT was based on the meta-analysis of all studies rather than the Bristol studies alone, specificity increased by 2%, sensitivity decreased by 0.2%, the total cost across all NIPT strategies reduced, but total QALYs were only marginally affected. PP1 and PP3 remained the most cost-effective strategies.

4.43 In a sensitivity analysis on the rates of inconclusive results, NIPT became less cost effective as the rate of inconclusive results increased, but strategies PP1 and PP3 always remained more cost effective than current practice. When the rate of inconclusive results was low, PP3 became the most cost-effective strategy. When the rate of inconclusive results was high, PP1 became the most cost-effective strategy.

4.44 A 2-way sensitivity analysis was done on test and treatment costs. The unit cost of NIPT is subject to uncertainty because it depends on throughput (the annual total number of samples analysed) and the level of the royalty fee. Similarly, the cost of anti-D immunoglobulin may differ from the list price depending on negotiated discounts. The results of a 2-way analysis on these unit costs showed that the base case is very sensitive to both the price of NIPT and the price of anti-D immunoglobulin. A small increase in price of high-throughput NIPT or a small fall in the price of anti-D immunoglobulin would result in current practice becoming more cost effective than NIPT strategies.

4.45 The cost of high-throughput NIPT for fetal *RHD* genotype was uncertain when this diagnostics guidance was written because it is highly dependent on the number of tests processed. The external assessment group did a threshold analysis to identify the point at which the test would move from being considered cost effective to being considered not cost effective, using a maximum acceptable ICER of £20,000 per QALY gained. Results show that raising the cost for high-throughput NIPT to £24.64 or more would result in current practice becoming more cost effective than NIPT strategies.

4.46 A sensitivity analysis was done on the cost of fetomaternal haemorrhage testing. Reducing the cost of a fetomaternal haemorrhage test to £3.17 (Szczepura et al. 2011; updated to 2015 prices) halved the estimated total costs of all strategies when compared with the total costs of the base-case scenarios, with total QALYs remaining similar to base-case results. When the cost of fetomaternal haemorrhage test was reduced, PP2 and PP4 became less cost effective than current practice, whereas PP1 and PP3 remained more cost effective compared with current practice.

4.47 An alternative postpartum-testing strategy to those included in the scope was assessed. The strategy separated women in whom NIPT identified a D-positive fetus from women in whom NIPT gave an inconclusive result (and were therefore treated as if the fetus was D-positive). Cord blood typing was done for women identified as having either a D-negative fetus by NIPT or who had an inconclusive NIPT result, but not done for women in whom NIPT indicated a D-positive fetus, and

resulted in total costs of £15,230,372 and £2,433,756 QALYs per 100,000 pregnancies. This postpartum approach dominated all other NIPT strategies, and the ICER for this strategy compared with current practice was £1,638,356 saved per QALY lost.

5 Committee discussion

Current practice

5.1 The committee considered the current standard of care offered to pregnant women who are rhesus-D (D) negative. It heard from clinical experts on the committee that current care for women who are not sensitised to the D antigen involves routine antenatal anti-D prophylaxis, additional doses of anti-D immunoglobulin if a woman has a potentially sensitising event, and postpartum testing of cord blood and anti-D prophylaxis if cord blood typing shows the baby to be D positive. The committee noted that introducing these methods for preventing sensitisation of women to the D antigen has dramatically reduced the number of sensitisations and the rates of haemolytic disease of the fetus and newborn over the last 40 years. The committee also heard from a clinical expert that there are effective treatments for D-negative women who are sensitised to D antigen, which means that deaths from severe haemolytic disease of the fetus and newborn are very rare.

5.2 The committee considered whether there were any problems with the current care offered to pregnant women who are D negative and not sensitised to the D antigen. It heard from a clinical expert that errors do sometimes occur, for example, a small number of women at risk of sensitisation do not have anti-D immunoglobulin, or do not receive the correct dose of anti-D immunoglobulin at the correct time. The committee also heard from a clinical expert that many sensitisations result from clinically silent fetomaternal haemorrhage events – potentially sensitising events without a known cause or clinical symptoms. The committee further heard that cord blood typing to determine the Rh blood group of the baby after birth may be affected by errors, such as sampling the blood of the mother instead of the baby, or incorrect sample labelling. The committee concluded that although anti-D prophylaxis is very effective for reducing sensitisations and therefore haemolytic disease of the fetus and newborn, it is not perfect because sensitisations do still happen.

5.3 The committee considered the possible disadvantages of using anti-D immunoglobulin. It heard from experts that there have previously been shortages of supply because it is a blood product and therefore a finite resource. The committee also considered the potential future risks from unknown prions or pathogens associated with using a blood product such as anti-D immunoglobulin. The committee concluded that it would be beneficial to conserve supplies by only using anti-D immunoglobulin for those in whom it is necessary.

5.4 The committee heard from a patient expert that for some women, having anti-D immunoglobulin may not be acceptable for personal, cultural or religious reasons. It noted that using high-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* genotype would allow women whose fetus was identified as D negative to avoid having unnecessary anti-D immunoglobulin, while women identified as having a D-positive fetus would be able to make an informed decision about whether to have anti-D immunoglobulin.

Clinical effectiveness

5.5 The committee considered the diagnostic performance of high-throughput NIPT for fetal *RHD* genotype. It noted that good-quality evidence was available and that the test is accurate after 11 weeks of gestation. The committee then considered how the diagnostic accuracy of the test affected clinical effectiveness. It noted that there is a small increase in the false-negative rate for high-throughput NIPT to determine fetal *RHD* genotype (0.21%; 95% CI [confidence interval] 0.09 to 0.48), compared with the current practice of postpartum cord blood typing. This means that some women with a D-positive fetus would be incorrectly identified as having a D-negative fetus and would not be offered routine antenatal anti-D prophylaxis (RAADP) or anti-D immunoglobulin after potentially sensitising events. Because of this, more women could become sensitised to the D antigen and may have complications in later pregnancies, although the committee heard from a clinical expert that the severity of these complications is hard to predict. The committee noted that the rate of sensitisations with current practice was estimated to be 281 per 100,000 D-negative pregnancies. If offering RAADP and anti-D immunoglobulin after potentially sensitising events

was based on the results from NIPT for fetal *RHD* genotype, the rate of sensitisations would increase by 3, to 284 sensitisations per 100,000 D-negative pregnancies. The committee considered that this relatively small increase in the number of sensitisations could be accepted in the context of other potential benefits of NIPT associated with avoiding unnecessary treatment with blood products.

5.6 The committee considered the results of the economic model. It noted that the quality-adjusted life year (QALY) losses in the model were 0.46 per 100,000 pregnancies if the postpartum testing strategy stayed the same as current practice (cord blood typing for all D-negative women regardless of the NIPT result). The committee noted that although this is a reduction in clinical effectiveness compared with current practice, the reduction is extremely small (0.0000046 QALYs per pregnancy). The committee therefore concluded that the clinical effectiveness of using high-throughput NIPT for fetal *RHD* genotype to guide antenatal anti-D prophylaxis is comparable with offering antenatal anti-D prophylaxis to all D-negative women, provided that there are no changes to postpartum practice.

Cost effectiveness

5.7 The committee considered the cost savings in the economic model. It noted that cost savings in the models were £583,538 per 100,000 pregnancies in D-negative women if the postpartum testing strategy stayed the same as current practice (cord blood typing for all D-negative women regardless of the NIPT result, referred to as postpartum scenario 1 [PP1] in the economic analysis). The committee noted that the cost savings are relatively small, at £5.84 per pregnancy, and on their own might not justify the risks that could be associated with making substantial changes to current practice. The committee then considered the base-case incremental cost-effectiveness ratio (ICER) for PP1. It noted that although the ICER appears to be large, at £1,269,100 saved for each QALY lost, it is very sensitive to changes in the numerator (change in cost) or denominator (change in QALYs), and is therefore subject to substantial uncertainty. The committee concluded that the total costs for using high-throughput NIPT for fetal *RHD* genotype to guide antenatal anti-D prophylaxis are not substantially different from the total costs for

the current practice of offering antenatal anti-D prophylaxis to all D-negative women, provided that there are no changes to postpartum practice.

5.8 The committee considered the different postpartum testing strategies presented in the diagnostics assessment report (see section 4.24). It noted that in the base-case analysis, NIPT using PP1 was the most cost-effective strategy compared with current practice. The committee heard from clinical experts that the postpartum care in PP1 is the same as used in current clinical practice. It also noted that with different assumptions on postpartum testing, other postpartum scenarios could be associated with greater cost savings, but increased QALY losses compared with PP1. The committee concluded that it is preferable to minimise the QALY losses.

5.9 The committee considered the results of a scenario analysis that made different assumptions on postpartum testing (PP5). It noted that this postpartum scenario was associated with greater cost savings and equivalent QALY losses compared with PP1. The committee heard from clinical experts that postpartum testing involves taking a cord blood sample soon after the birth, and that although midwives are used to doing this they also have multiple other tasks to complete at this time. The committee was concerned that if midwives had to get the NIPT result and then make a decision on whether to take a cord blood sample in the period immediately after the delivery, errors could be made, for example, not taking a cord blood sample from a fetus predicted to be D negative. The committee concluded that although alternative postpartum strategies may potentially have greater cost savings, they would be complicated to implement in clinical practice and may result in errors, which could affect costs and clinical effectiveness. The committee also discussed an alternative approach in which cord blood samples would be taken from all babies born to D-negative women and the laboratory would then decide whether to test the cord blood sample. The committee concluded that the postpartum testing of cord blood should not be changed from current practice. This is because without cord blood typing, false-negative NIPT results would not be identified and women with false-negative NIPT results would not have postpartum anti-D prophylaxis. The committee noted the difficulties of taking a blood

sample from the cord and that the consequences of a sampling error may include having to take repeat blood samples from a neonate. It decided that further research on the practicalities of implementing alternative postpartum testing strategies would be valuable (see section 6.2).

5.10 The committee discussed the input used in the model for the cost of care of a pregnant woman who has been sensitised to the D antigen in an earlier pregnancy. It heard from a clinical expert that some women who are sensitised to the D antigen will be identified as having a D-negative fetus, and others will be identified as having a D-positive fetus, but will not experience problems during their pregnancy. These 2 groups of women would not need many extra appointments with a specialist obstetrician. A third group of sensitised women will be identified as having a D-positive fetus and will experience problems during their pregnancy. These women will need more frequent surveillance and treatment for the baby before and after the birth. The committee concluded that if a weighted average is taken of the cost of care for these 3 groups of pregnant women, then an input of £3,167 per sensitised pregnancy is reasonable.

5.11 The committee considered the cost of the test that was used in the economic model and noted that the cost did not include sample transport. It heard from the current provider of the test, the International Blood Group Reference Laboratory (IBGRL), that blood samples are transported around the country to their laboratory on a daily basis using the NHS Blood and Transplant (NHSBT) transport network. It heard further, that because of this established transport network, there should be no cost for sample transport. The committee was concerned that although there may be no cost for sample transport between the NHSBT units and the IBGRL, there may be a cost for transporting the sample from the maternity clinic to the NHSBT unit. It was also concerned about the length of time it may take to transport samples from rural areas to the IBGRL, and that longer sample transport times may result in increased rates of failed tests. The committee also heard from the IBGRL that the unit cost of the test depends on the expected annual sample throughput and on a royalty fee, which is currently under negotiation. The committee concluded that the test cost is uncertain.

5.12 The committee considered whether there were any costs associated with implementing high-throughput NIPT for fetal *RHD* genotype that had not been included in the economic model. It noted that extra time to explain the test, take the blood sample, give the test results, and provide counselling, that could result in extra midwife appointments, were not included in the model. The committee heard from a clinical expert that in the south-west of England where high-throughput NIPT for fetal *RHD* genotype has been implemented, the blood sample for the test is normally taken at the routine 16-week antenatal appointment; therefore, no additional appointments are needed. It also heard from the clinical expert that the main issue when implementing the test was educating midwives and other healthcare professionals so they understood the test and could explain it to women and their families. It noted that a patient information leaflet explaining the test and its results is available from NHSBT. The committee heard from the external assessment group that none of the studies in the review of implementation, included costs associated with implementation. The committee concluded that the costs associated with implementing high-throughput NIPT for fetal *RHD* genotype were uncertain.

5.13 The committee considered a threshold analysis done by the external assessment group on the unit cost of the test. It noted that results show that the cost effectiveness of high-throughput NIPT for fetal *RHD* genotype is sensitive to small increases in costs associated with doing the test, for example, sample transport, the need for repeat tests, midwife time, or the cost of the test itself. The committee also noted that increasing the test cost to £24.64 or more per test would result in high-throughput NIPT for fetal *RHD* genotype no longer being cost effective compared with current practice, using a maximum acceptable ICER of £20,000 per QALY gained. The committee concluded that high-throughput NIPT for fetal *RHD* genotype has the potential to be cost effective, but that the cost savings are volatile with respect to the cost of the test (see section 5.11) and the costs associated with implementation (see section 5.12). The committee also concluded that the overall cost of testing below which high-throughput NIPT for fetal *RHD* genotype can be considered cost effective should not be stated to 2 decimal places in the recommendation. This is because there is substantial uncertainty about the results of the model. The committee decided that £24.64 should be

rounded down to £24 rather than up to £25 to increase the chance of high-throughput NIPT for fetal *RHD* genotype being cost effective.

Other considerations

5.14 The committee noted its conclusions on the comparable clinical effectiveness of high-throughput NIPT for fetal *RHD* genotype and current practice (see section 5.6), and the uncertainty about cost savings (see section 5.13). The committee also noted its conclusion that it would be beneficial to avoid inappropriate use of anti-D immunoglobulin (see section 5.3). The committee decided that although the cost savings are potentially small, recommending high-throughput NIPT for fetal *RHD* genotype would be an effective way of reducing unnecessary use of anti-D immunoglobulin, and that this reduction could affect a large number of women.

5.15 The committee considered the effect that ethnicity has on NIPT results. They heard from the provider of the test, IBGRL, that D-negative women of black African family origin are more likely to have an *RHD* pseudogene, and so are more likely to have an inconclusive or false-positive NIPT result compared with women from other ethnic family origins. The committee noted that women with an inconclusive or false-positive NIPT result would be offered antenatal anti-D prophylaxis (that is, they would have the same care as they would have in current practice), and so would not be at a greater risk of sensitisation to the D antigen than women from other ethnic family origins. It noted further that although unnecessary anti-D immunoglobulin use would be reduced in women of black African family origin, these women would be more likely to have unnecessary anti-D immunoglobulin than women of white European family origin. The committee concluded that this is a proportionate means of achieving a reduction in anti-D immunoglobulin use in the population as a whole.

5.16 The committee considered the current level of interest in high-throughput NIPT for fetal *RHD* genotype. It heard from a clinical expert that there have been many enquiries about the test from healthcare professionals and women who would like to have the test but do not live in an area where it has been implemented. It also heard from another

clinical expert that the level of knowledge and understanding of NIPT is growing because of the publicity around NIPT for Down's syndrome and other aneuploidies. The committee concluded that based on the current level of interest, the timing was right for making a recommendation of high-throughput NIPT for fetal *RHD* genotype, but noted that additional data collection from areas beginning to implement the test would help confirm the cost of implementing the test given the uncertainty about this.

6 Recommendation for further research

6.1 Data collection and analysis of the costs and resource use associated with implementing high-throughput non-invasive prenatal testing for fetal *RHD* genotype is recommended to show the overall cost of testing and to inform any future update of the guidance. This may include costs and resource use associated with:

- training for healthcare professionals
- explaining the test to women and their families
- test failures
- blood sampling, giving results and counselling when needed
- sample transport and management
- record keeping
- adherence to high-throughput non-invasive prenatal testing and antenatal anti-D prophylaxis.

6.2 Further research is recommended on alternative postpartum testing strategies that do not include cord blood typing of all babies born to rhesus-D (D) negative women. This may include:

- an audit of D results from cord blood typing compared with results from high-throughput NIPT for fetal *RHD* genotype
- research on the practicalities of implementing alternative postpartum testing strategies.

7 Implementation

NICE has developed tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

- Adoption support resource

In addition NICE will support this guidance through a range of activities to promote the recommendation for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendation in section 6 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

8 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Professor Adrian Newland
Chair, diagnostics advisory committee and Professor of Haematology, Barts Health NHS Trust

Dr Mark Kroese
Vice Chair, diagnostics advisory committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Ron Akehurst
Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Mr John Bagshaw
In Vitro Diagnostics Consultant

Dr Phil Chambers
Research Fellow, Leeds Institute of Cancer and Pathology, University of Leeds

Dr Sue Crawford
GP Principal, Chillington Health Centre

Professor Erika Denton
National Clinical Director for Diagnostics, NHS England; Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards
Head of Health Technology Assessment, British Medical Journal (BMJ) Evidence Centre

Dr Simon Fleming
Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Dr James Gray
Consultant Microbiologist, Birmingham Children's Hospital

Mr John Hitchman
Lay member

Professor Chris Hyde
Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Mr Patrick McGinley
Head of Costing and Service Line Reporting, Maidstone and Tunbridge Wells NHS Trust

Dr Michael Messenger
Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

Mrs Alexandria Moseley
Lay member

Dr Peter Naylor
GP, Chair, Wirral Health Commissioning Consortia

Dr Dermot Neely
Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Dr Simon Richards
Vice President Regulatory Affairs, Europe and Middle East (EME), Alere Inc

Dr Deirdre Ryan
Consultant Cellular Pathologist, Royal London Hospital

Professor Mark Sculpher
Professor of Health Economics, Centre for Health Economics, University of York

Dr Steve Thomas
Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals Foundation Trust

Professor Anthony Wierzbicki
Consultant in Metabolic Medicine/Chemical Pathology, St Thomas' Hospital

Specialist committee members

Mrs Joanna Davis
Senior Antenatal Screening Specialist, Nottingham University Hospitals NHS Trust

Ms Jenny Ford
Midwifery Matron, University Hospitals Bristol NHS Foundation Trust

Dr Ruth Gottstein
Consultant Neonatologist, Central Manchester University Hospitals NHS Foundation Trust

Dr Alec McEwan
Consultant Obstetrician and Subspecialist in Fetal Medicine, Nottingham University Hospitals NHS Trust

Dr Samantha Revill
Lay specialist committee member

Dr Susan Robinson
Consultant Haematologist, Guy's and St Thomas' NHS Foundation Trust

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Frances Nixon
Topic Lead

Rebecca Albrow
Technical Adviser

Robert Fernley
Project Manager

9 Sources of evidence considered by the committee

The diagnostics assessment report was prepared by CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York.

- Yang H, Saramago Goncalves P, Llewellyn A, et al. High-throughput, non-invasive prenatal testing for fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen: a systematic review and economic evaluation. May 2016.

Registered stakeholders

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report and the diagnostics consultation document.

Provider of technologies included in the final scope:

- International Blood Group Reference Laboratory

Other commercial organisations:

- CSL Behring UK Ltd

Professional groups and patient/carer groups:

- British Maternal and Fetal Medicine Society
- British Society for Haematology
- Royal College of Nursing
- Royal College of Physicians

Research groups:

- None

Associated guideline groups:

- None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government

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Accreditation