National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

High-throughput non-invasive prenatal testing for fetal rhesus-D status

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read in conjunction with the final scope issued by NICE for the assessment and the diagnostics assessment report. A glossary of terms can be found in appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical effectiveness and cost effectiveness of high-throughput non-invasive prenatal testing (NIPT) for fetal rhesus D (RhD) status. The test involves analysing cell-free fetal DNA in maternal blood and is intended for use in pregnant women who are RhD negative and are not sensitised to RhD antigen.

During pregnancy small amounts of fetal blood can enter the maternal circulation (an event called fetomaternal haemorrhage). The presence of fetal RhD-positive cells in the maternal circulation, after fetomaternal haemorrhage, can cause a mother who is RhD negative to produce antibodies against the RhD antigen (anti-D antibodies) – a process is 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.

The process of sensitisation has no adverse health effects for the mother and usually does not affect the pregnancy during which it occurs. But, if the mother is exposed to the RhD antigen, from an RhD-positive fetus during a later 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 if RhD-negative pregnant women have anti-D immunoglobulin. NICE technology appraisal guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative recommends anti-D immunoglobulin for all pregnant women who are RhD negative and who are not known to be sensitised to the RhD antigen, because the RhD status of the baby is unknown. This routine antenatal anti-D prophylaxis (RAADP) can be given as 2 doses (one at 28 weeks and one at 34 weeks' gestation), or as a single dose between 28 and 30 weeks' gestation. 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 also recommends that all RhD-negative pregnant women who are not known to be sensitised to RhD antigen have anti-D immunoglobulin:

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

Anti-D immunoglobulin is produced from the pooled plasma donated by large numbers of RhD-negative people who have had a transfusion of RhD-positive red cells to stimulate the production of RhD antibodies, and so carries a small risk of transmission of human blood-borne viral or prion diseases.

High-throughput NIPT for fetal RhD status may allow anti-D immunoglobulin to be withheld from RhD-negative women who are carrying an RhD-negative

fetus. These women could avoid unnecessary treatment with anti-D immunoglobulin, as well as the slight risk associated with blood products.

High-throughput NIPT for fetal RhD status may allow RhD-negative women who are carrying an RhD-positive fetus 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.

Provisional recommendations on using this technology will be formulated by the diagnostics advisory committee at the committee meeting on 15 June 2016.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does high-throughput NIPT for fetal RhD status represent a clinical- and cost-effective use of NHS resources?
Populations	Pregnant women who are RhD negative and are not sensitised to RhD antigen
Intervention	High-throughput NIPT for fetal RhD 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 women who are RhD negative and not sensitised who accept the test • number of doses of anti-D immunoglobulin given (routine antenatal, after 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 later 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 after potentially sensitising events • anti-D immunoglobulin, associated administration costs and treatment of adverse effects • costs of post-delivery testing • cost of hospital stay after birth (length of stay) • costs of managing future pregnancies when sensitisation has occurred • costs associated with treating haemolytic disease of the fetus and newborn
	The cost effectiveness of interventions should be expressed as 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.

Further details including descriptions of the intervention, care pathway and outcomes can be found in the final scope.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group.

2.1 Clinical effectiveness

The external assessment group carried out systematic reviews of the evidence on the diagnostic accuracy and clinical effects of high-throughput NIPT for fetal RhD status. Details of the systematic reviews are in the diagnostics assessment report (from page 31). The objectives of systematic reviews were to review:

- the diagnostic accuracy of high-throughput NIPT for detecting RhD-positive fetuses
- the clinical effectiveness of high-throughput NIPT for fetal RhD status, including number of sensitisations, test adherence and incidence of adverse events
- the implementation of high-throughput NIPT for fetal RhD status in countries or regions where it has been used, examining feasibility, guidance or recommendations for practice, and the need for further research
- existing systematic reviews of anti-D immunoglobulin treatment, identifying number of sensitisations, adherence and incidence of adverse events (this review was used for the clinical- and cost-effectiveness modelling).

In total, 14 studies from 45 reports were included in the external assessment group's review. Of these, 8 reported on diagnostic accuracy, 7 on clinical effectiveness, and 12 on implementation. Four systematic reviews that provided data used for simulating clinical effectiveness were also identified.

Evidence on diagnostic accuracy

Study characteristics and critical appraisal

There were 8 studies that reported the diagnostic accuracy of high-throughput NIPT for fetal RhD status, all of which were prospective studies carried out in European countries (table 2). Four studies were done in England, 3 of which were based in Bristol (UK).

Table 2 Characteristics of the diagnostic accuracy studies

Study	Location	Gestational age at time of NIPT (weeks; median/range)	Sample size[1]	RhD-positive fetuses	RhD-negative fetuses	Inconclusive test results
Akolekar et al. 2011	UK (London)	12.4 (11–14)	586	410	176	84
Banch Clausen et al. 2014	Denmark	25 (23–28)	12,668	7,830	4,838	274
Chitty et al. 2014	UK (Bristol)	19 (5–35)	4,913	2,890	2,023	393
Finning et al. 2008	UK (Bristol)	28 (8–38)	1,869	1,156	713	64
Grande et al. 2013	Spain	24–26	282	186	96	Not reported
Soothill et al. 2015	UK (Bristol)	15–17 (mostly)	499[2]	315	184	61
Thurik et al. 2015	Netherlands	26	18,383[2]	11,283	7,100	Not reported
Wikman et al. 2012	Sweden	8–40	3,291[3]	2,073	1,218	13

[1] Number of blood samples unless otherwise specified

[2] Number of participants

[3] Excludes pre-8 weeks gestation pregnancies

Abbreviation: NIPT, non-invasive prenatal testing.

All 8 full text papers were assessed for risk of bias using a modified version of the QUADAS-2 tool containing 14 items. Most studies were considered to be at low risk of bias. Because NIPT was run on automated platforms it was deemed at limited risk of human error, and multiple controls were used for RHD assays in all except 1 study (Wikman et al. 2012). Cord blood typing was the reference standard in all studies. The index test of NIPT was done independently of the reference standard and the results of one were considered unlikely to influence the results of the other, so the risk of incorporation bias was considered low.

Two studies (Akolekar et al. 2011; Thurik et al. 2015) were judged to be at high risk of bias. The study by Akolekar et al. (2011) stated that the targeted RhD-negative women were selected from a database, but it was unclear whether this selection was done on a random basis. It reported a high rate of inconclusive results (15%), and excluded these inconclusive results from its analyses, possibly inflating its diagnostic accuracy estimates. Characteristics of the reference standard were also poorly reported. Thurik et al. (2015)

excluded multiple pregnancies from the analysis, and only 80% of participants had a reference standard. Reasons why cord blood typing was not carried out in a significant proportion of the study population were not reported. The study also stated that the prediction algorithm was judged daily and adjusted as needed, which is likely to have introduced bias in the diagnostic accuracy estimates.

Except for 2 studies, the results of the studies were considered broadly applicable to using high-throughput NIPT for fetal RhD status for nationwide testing in the UK. The test used by Wikman et al. (2012) only targeted exon 4, unlike all other included studies, which targeted at least 2 exons. Also, most participants in Wikman et al. (2012) had NIPT in the first trimester of pregnancy, when NIPT for fetal RhD status is less accurate. The study by Akolekar et al. (2011) recruited a large proportion of women of African family origin (19.3%), which may not be representative of the general population of pregnant women in the UK.

Diagnostic-accuracy results

An important issue relating to the diagnostic accuracy of NIPT is what happens after women have inconclusive test results. It is expected that, in the UK, such women will be treated as having a positive test with no further testing. Data on inconclusive tests 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 studies only done in Bristol.

In all analyses, women in whom NIPT was carried out at or before 11 week's gestation were excluded because the test is known to be less accurate before 11 weeks (see below).

Because NIPT for fetal RhD status is highly accurate, the results are presented with the focus on incorrect test results; that is, the false-positive rate (incorrectly testing positive, and so offered unnecessary anti-D immunoglobulin) and the false-negative rate (incorrectly testing negative, and so at risk of sensitisation and do not have anti-D immunoglobulin). Results of the hierarchical bivariate meta-analyses are shown in table 3.

Table 3 Meta-analysis results

Analysis case	**Number of studies**	**False-negative rate (at risk of sensitisation)**		**False-positive rate (unnecessary anti-D)**	
		Estimate (%)	95% CI	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.					

NIPT for fetal RhD status is very accurate among women with an RhD-positive fetus; only 2 to 4 in 1000 such women will have a negative test result and so be at risk of sensitisation due to not being offered anti-D immunoglobulin. NIPT for fetal RhD status is slightly less accurate among women with an RhD-negative fetus; between 1.3% and 5.7% of such women will test positive (depending on the type of analysis), and so may be offered anti-D immunoglobulin unnecessarily. When women with inconclusive test results were excluded from analyses, the false-positive rate was 1.3%.

The analysis of the 3 Bristol studies gave a slightly lower false-negative rate and a higher false-positive rate 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.

Inconclusive test results

Treating inconclusive test results as if they were a positive test has a substantial effect on diagnostic accuracy. Table 4 summarises the rates of inconclusive test results across the included studies.

Table 4 Inconclusive test results in the included studies

Study	Location	RhD-positive fetuses (%)	Inconclusive test results (%)	RhD-positive fetuses in women with inconclusive test results (%)
Akolekar et al. 2011	UK (London)	70.0	14.3	85.7
Banch Clausen et al. 2014	Denmark	61.8	2.2	66.8
Chitty et al. 2014	UK (Bristol)	58.8	7.0	76.6
Finning et al. 2008	UK (Bristol)	61.9	3.4	54.7
Grande et al. 2013	Spain	66.0	Not reported	
Soothill et al. 2015	UK (Bristol)	63.1	12.2	77.0
Thurik et al. 2015	Netherlands	61.4	Not reported	
Wikman et al. 2012	Sweden	63.0	0.4	38.5

Results show there is considerable variation in rates of inconclusive tests across studies. 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 African family origin). But, even in the studies in which tests were done in Bristol and all using the same test, there is considerable unexplained variation.

Results also show that, in general, most women with an inconclusive test result have an RhD-positive fetus, and so treating all women with inconclusive test results with anti-D immunoglobulin may be considered reasonable, if no further testing is possible.

A meta-analysis was carried out to estimate average rates of inconclusive test results (table 5). Based on these results it is estimated that 6.7% of women in the UK would have an inconclusive test result.

Table 5 Meta-analysis of inconclusive test result

Studies included	Estimated inconclusive rate	95% confidence interval
All reporting inconclusive tests	4.0%	1.5–10.3
Bristol studies only	6.7%	3.7–11.7

Timing of testing

The effect of the timing of high-throughput NIPT for fetal RhD status on diagnostic accuracy was considered. The analysis suggested that false-negative rates were higher before 11 weeks' gestation, and that after 11 weeks' gestation false-negative rates were consistent, irrespective of timing. There was no obvious correlation between false-positive rates and gestational age at the time of high-throughput NIPT. Chitty et al. (2014) examined test performance at multiple time points and found that false-negative rates were higher before 11 week's gestation, and were generally stable after 11 weeks' gestation.

The effect of the timing of high-throughput NIPT on the number of inconclusive test results was also considered. There appears to be a trend that the percentage of inconclusive results for this test drops as the gestational age increases from 11 weeks.

Evidence on clinical outcomes

Study characteristics and critical appraisal

Seven studies reported the clinical effectiveness of NIPT for fetal RhD status (table 6), 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. Most studies recruited women with a median gestational age of 10 to 26 weeks.

Table 6 Characteristics of clinical-effectiveness studies

Study	Location	Study dates	Sample size[1]	Gestational age at time of NIPT (weeks)	Comparator
Banch Clausen et al. (2014)	Denmark, 1 region	01/2010 to 06/2010	591	25 (median)	Postpartum anti-D only (n=109)
Banch Clausen et al. (2012)	Denmark, nationwide	01/2010 to 06/2010	2312	25 (median)	None
Damkjaer et al. (2012)	Denmark, 1 hospital	06/2010 to 09/2010	239	27 (mean)	None
de Haas et al. (2012)	Netherlands, nationwide	07/2011 to 01/2012	15126[2]	26 (mean)	None
Grande et al. (2013)	Spain, Barcelona	02/2010 to 10/2011	284	24–26 (range)	None
Soothill et al. (2015)	England, 3 NHS Trusts in south west England	04/2013 to 09/2013	529	15–26 (range)	None
Tiblad et al. (2013)	Sweden, Stockholm area	09/2009 to 03/2012 (reference cohort: 2004 to 2008)	8,347[3]	10 (3–40)	Postpartum anti-D only (historical control; n=18,546)

[1] Number of blood samples tested using NIPT unless otherwise specified

[2] Number of participants having NIPT

[3] Number of pregnancies in which NIPT was done

Abbreviation: NIPT, non-invasive prenatal testing

Only 2 studies compared women having NIPT for fetal RhD status with controls (Tiblad et al. 2013; Banch Clausen et al. 2014). Tiblad et al. (2013) compared patients having NIPT, routine care with no NIPT, and routine postpartum anti-D prophylaxis only (historical control). Banch Clausen et al. (2014) reported data on anti-D immunoglobulin adherence in a small subgroup of participants from 1 region in Denmark, comparing participants having NIPT with those that did not have NIPT.

The quality of these 2 comparative studies was assessed using the ACROBAT-NRSI tool, and both were assessed as having significant limitations. Tiblad et al. (2013) was considered to be at serious risk of bias, mainly because of concerns about patient selection, confounding and missing data. Banch Clausen et al. (2014) was considered to be at critical risk of bias because of concerns about patient selection and lack of adjustment for

potential confounders. 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 status. A formal quality assessment of these studies was not carried out because evidence from non-controlled studies was considered to be of poor quality.

A narrative synthesis was presented because of the heterogeneity in outcomes and study designs.

Evidence on sensitisations

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 RhD sensitisation in the cohort that had high-throughput NIPT for fetal RhD status as 0.26 % (95% confidence interval [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 status 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 (postpartum anti-D prophylaxis only). 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).

Evidence on NIPT for fetal RhD status uptake

Seven studies reported uptake rates of NIPT for fetal RhD status (table 7). 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 status. The only country that reported nationwide uptake data was the Netherlands, where

more than 95% of eligible women had NIPT for fetal RhD status. The studies generally noted that uptake is likely to increase over time if a nationwide screening programme is implemented.

Table 7 Uptake of NIPT for fetal RhD status

Study	Rates of NIPT uptake	Country
Banch Clausen et al. 2014	84.2% (581/690)	Denmark
Chitty et al. 2014	88% (372/3,069)	England
Damkjaer et al. 2012	90% (215/ 239)	Denmark
De Haas et al. 2012	>95% (15126/ approx. 15,750)	Netherlands
Grande et al. 2013	94% (284/302)	Spain
Soothill et al. 2015	70% (approximately)	England
Tiblad et al. 2013	89% (8374/9,380)	Sweden
Abbreviation: NIPT, non-invasive prenatal testing.		

Evidence on routine antenatal anti-D prophylaxis uptake

The uptake of RAADP in women who accepted NIPT and had a positive result was reported in 4 studies (table 8). 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). Van der Ploeg et al. (2015) reported nationwide data on women having NIPT for fetal RhD status 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 status, 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.

Table 8 Routine antenatal anti-D prophylaxis uptake

RAADP	% (n/N)	Source	Country
Uptake of RAADP with no NIPT (current practice)	99% (N=5,276) having at least 1 injection 87.5% (N=5,276) having the correct dose at the correct time	UK anti-D audit[2]	UK

	90%[1] (NR/5,276) having all injections at correct doses		
	100% (10/10)	Soothill et al. 2015	England
Uptake of RAADP in those who refuse NIPT	0 (0/23)	Damkjaer et al. 2012	Denmark
	80% (4/5)	Soothill et al. 2015	England
Uptake of RAADP in those who accept NIPT and have a positive result	93.2% (330/354)	Banch Clausen et al. 2014	Denmark
	86% (NR)	Damkjaer et al. 2012	Denmark
	90% (4,590/5,104)	Tiblad et al. 2013	Sweden
	96.1% (of about 18,383)	Van der Ploeg et al. 2015	Netherlands
Uptake of RAADP in those who accept NIPT and have an inconclusive result	100% (5/5)	Soothill et al. 2015	England
Uptake of RAADP in those who accept NIPT and have a negative result	6% (1/18)	Soothill et al. 2015	England
	5% (5/95)	Grande et al. 2013	Spain
[1] Full adherence (correct dose, correct time) to single-dose regimen. 99% had at least 1 dose. [2] Although this study did not meet the selection criteria for this review (no NIPT), it is included here for informative purposes			
Abbreviations: NIPT, non-invasive prenatal testing; NR, not reported; RAADP, routine antenatal anti-D prophylaxis.			

Evidence on postpartum anti-D prophylaxis uptake

The uptake of postpartum anti-D prophylaxis in women who accepted NIPT for fetal RhD status and had a positive result was reported in 3 studies (table 9). Data from these studies was 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). Van der Ploeg et al. (2015) reported nationwide data on women having NIPT for fetal RhD status 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.

Table 9 Postpartum anti-D prophylaxis uptake

Postpartum anti-D prophylaxis	% (n/N)	Source	Country
Uptake of postpartum anti-D with no testing	98.4% (91.6% correct dose and time) (NR/3392)	UK anti-D audit[1]	UK
	95.7% (66/69)	Banch Clausen et al. 2014	Denmark
Uptake of postpartum anti-D in those who refuse NIPT	>99% (NR)	Damkjaer et al. 2012	Denmark
Uptake of postpartum anti-D in those who accept NIPT and have a positive result	99.7% (353/354)	Banch Clausen et al. 2014	Denmark
	99.3% (151/152)	Damkjaer et al. 2012	Denmark
	92% (of approx. 18383)	Van der Ploeg et al. 2015	Netherlands
Uptake of postpartum anti-D in those who accept NIPT and have an inconclusive result	No data	Not applicable	Not applicable
Uptake of postpartum anti-D in those who accept NIPT and have a negative result	0 (0/227)	Banch Clausen et al. 2014	Denmark
	0 (0/85)	Damkjaer et al. 2012	Denmark
	0.087% (2/NR)	Banch Clausen et al. 2012	Denmark
	0 (NR)	Soothill et al. 2015	England
[1] Although this study did not meet the selection criteria for this review (no NIPT), it is included here for information.			
Abbreviations: NIPT, non-invasive prenatal testing; NR, not reported.			

Reduction in anti-D immunoglobulin use

Outcome measures relating to anti-D immunoglobulin administered were reported in 3 non-comparative studies. Soothill et al. (2015) reported a significant monthly 6% reduction in anti-D immunoglobulin administration (95% CI 4 to 8) within 6 months 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 RhD-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% women avoided unnecessary anti-D immunoglobulin within 2 years of the introduction of a programme of NIPT for fetal RhD status. Grande et al. (2013) reported that, of 95 women carrying an RhD-negative fetus, 5 women requested anti-D immunoglobulin; so, unnecessary anti-D immunoglobulin was avoided in 95% of women carrying an RhD-negative fetus.

Simulation study of clinical effectiveness

To better understand the likely consequences of implementing NIPT for fetal RhD status and basing anti-D immunoglobulin administration on its results, the external assessment group did a simulation study. Table 10 summarises the parameter estimates used in the simulation. The following assumptions were made:

- 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 administering anti-D immunoglobulin.

Table 10 Parameter estimates used in the simulation study

Probability	Estimate	Source
Diagnostic accuracy		
RhD-positive fetus	60.7%	Diagnostic meta-analysis (Bristol studies)
RhD-positive fetus (with inconclusive NIPT result)	70.7%	Diagnostic meta-analysis (Bristol studies)
False-negative NIPT result	0.21%	Diagnostic meta-analysis (Bristol studies)
Inconclusive NIPT result	6.7%	Diagnostic meta-analysis (Bristol studies)
False-positive test (if conclusive)	1.5%	Diagnostic meta-analysis (Bristol studies)[1]
Adherence		
Adherence to antenatal anti-D (without NIPT; had at least 1 dose of anti-D)	99%	UK 2013 audit
Uptake of NIPT	96%	De Haas et al. 2012
Adherence to postpartum anti-D	99%	UK 2013 audit
Adherence to antenatal anti-D (if NIPT refused or missed)	80%	Soothill et al. 2015
Adherence to antenatal anti-D (if NIPT inconclusive)	99%	Soothill et al. 2015
Uptake of antenatal anti-D in women with negative NIPT	6%	Soothill et al. 2015
Adherence to postpartum anti-D after NIPT process	99%	No data. Assumed same as without NIPT
Outcomes		
Sensitisation with antenatal anti-D and postpartum anti-D	0.35%	Pilgrim et al. 2009
Sensitisation with only postpartum anti-D	0.95%	Pilgrim et al. 2009
Sensitisation with no anti-D	10.7%	Pilgrim et al. 2009, and Crowther et al. 1997
Sensitised women having a further pregnancy in	62%	Used by Chitty et al. 2014, no source given

Death of RhD-negative fetus in sensitised women	5%	Used by Chitty et al. 2014, no source given
[1] Based on a diagnostic meta-analysis of the Bristol-based studies, excluding women with inconclusive test results (result not reported in the main body of the diagnostic assessment report)		

The results of the simulation study, summarised in table 11, showed that using NIPT for fetal RhD status leads to a substantial reduction in RAADP use, from 99% of RhD-negative women to 65.9%.This decline is similar in size to that seen by Soothill et al. (2015). The decrease is a because of the drop (from 39% to 5.7%) in women with RhD-negative fetuses needlessly having anti-D immunoglobulin. Using NIPT for fetal RhD status means that about 1.2% of women miss having possibly beneficial RAADP, compared with 0.6% for a universal RAADP approach.

Table 11 Results of the simulation study

Outcome	Treatment approach	Proportion of women
Antenatal anti-D prophylaxis		
Antenatal anti-D given	Universal anti-D	99%
	Based on NIPT	65.9%
Unnecessary anti-D given (RhD-negative fetus)	Universal anti-D	38.9%
	Based on NIPT	5.7%
Anti-D not given (RhD-positive fetus)	Universal anti-D	0.6%
	Based on NIPT	1.2%
Sensitisations		
Sensitised during or after pregnancy	Postpartum/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%
Deaths because of sensitisations		
Deaths in later pregnancies	Postpartum/emergency anti-D only	0.0198%
	Universal anti-D	0.0086%
	Based on NIPT with postpartum anti-D	0.0091%
	Based on NIPT with no postpartum anti-D for women testing negative	0.0091%
Abbreviation: NIPT, non-invasive prenatal testing.		

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 failure of anti-D immunoglobulin (around 284 per 100,000 women) and compared with not using RAADP at all (around 641 per 100,000).

Results of the simulation study also showed that using NIPT for fetal RhD status is unlikely to have any meaningful effect on mortality in later pregnancies. Even if postpartum anti-D prophylaxis is never given to women with a negative NIPT result, there would be about 5 extra deaths per 1 million RhD-negative women.

2.2 Costs and cost effectiveness

Systematic review of cost-effectiveness evidence

The external assessment group did a search to identify existing studies on the cost effectiveness of high-throughput NIPT to determine fetal RhD status in pregnant women who are RhD negative and are not sensitised to the RhD antigen. Full economic evaluations that compared 2 or more options and considered both costs and consequences were included in the review. A quality appraisal was carried out using the Drummond and Jefferson checklist. Full details of the review of existing cost-effectiveness evidence starts on page 74 of the diagnostic assessment report.

Results across the existing economic studies were conflicting. Three studies reported that NIPT for fetal RhD status was not cost-effective or was of no economic benefit. The main factor driving these results was the cost of the test itself, that is, the clinical and economic benefits were not sufficient to offset the additional costs of the test. Szczepura et al. (2011) also stated that implementing NIPT in the clinical pathway for RhD-negative pregnant woman was not expected to produce important clinical benefits.

Two studies reported that NIPT for fetal RhD status is cost-saving compared with no RAADP, that is, compared with postpartum anti-D prophylaxis only. Only 1 study found NIPT for targeting RAADP to be cost-saving compared

with non-targeted RAADP, which also estimated no increase in the risk of sensitisation if NIPT were to be used.

Overall, 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.

Only 1 of the economic studies directly relates to the UK (Szczepura et al. 2011). But this study did not explicitly explore how introducing NIPT for fetal RhD status could affect costs relating to potentially sensitising events. Also, it assumed that postpartum testing and treatment would be unaffected by NIPT results. Furthermore, no assessment of the timing of NIPT was done, and there was no consideration of the effect on later pregnancies.

Economic analysis

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

Model structure

A decision tree cohort approach was developed to estimate the costs and health outcomes with and without high-throughput NIPT for fetal RhD status. 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). A schematic representation of the model can be found on pages 96 and 97 of the diagnostics assessment report.

A pregnant woman enters the model after being identified as RhD negative and not sensitised to the RhD antigen, based on testing at first contact with the doctor or midwife, or at the booking appointment (at 8 to 12 weeks'

gestation). If the woman contacts the healthcare service after any potentially sensitising event she may be offered anti-D immunoglobulin and, if after 20 weeks' gestation, a fetomaternal haemorrhage test to see how much fetal haemoglobin has been released into the maternal circulation. Women provided with RAADP have it at either or both of the routine visits at 28 and 34 weeks' gestation. At delivery, a sample of cord blood may be taken and the baby's RhD status established to guide fetomaternal haemorrhage testing and postpartum anti-D prophylaxis.

The first part of the model divides the cohort according to fetal RhD status and treatment. This determines when having RAADP is appropriate, inappropriate, and unnecessary and when avoidance of RAADP is potentially harmful. Aspects such as the diagnostic test performance, compliance with high-throughput NIPT for fetal RhD status and RAADP, and the effectiveness of RAADP all inform the estimation of the probability of sensitisation for each of these groups. 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. Costs and utilities are then evaluated for the different components and for each of the alternative pathways.

Four alternative ways 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 status identified through high-throughput NIPT.
- Postpartum scenario 2 (PP2): postpartum cord blood typing, fetomaternal haemorrhage testing (and by implication anti-D immunoglobulin) would be withheld if high-throughput NIPT of fetal RhD status identifies an RhD-negative fetus, but would continue to be done if high-throughput NIPT was inconclusive or had identified an RhD-positive fetus.

- Postpartum scenario 3 (PP3): postpartum cord blood typing would be done if high-throughput NIPT of fetal RhD status identifies an RhD-negative fetus. Fetomaternal haemorrhage testing and post-delivery anti-D immunoglobulin would be provided high-throughput NIPT was inconclusive or identified an RhD-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 an RhD-positive fetus.

These different strategies are summarised in table 12.

Table 12 Characteristics of the postpartum strategies

Scenarios	High-throughput NIPT result	Cord blood typing	FMH	Postpartum anti-D
Postpartum scenario 1	Any	Yes	Yes if CS+	As guided by CB and FMH
Postpartum scenario 2	T-	No	No	No
	T+, inc	Yes	Yes if CS+	As guided by CB and FMH
Postpartum scenario 3	T-	Yes	Yes if CS+	As guided by CB and FMH
	T+, inc	No	Yes	Yes with additional dose per FMH
Postpartum scenario 4	T-	No	No	No
	T+, inc	No	Yes	Yes with additional dose per FMH
'-' indicates negative high-throughput NIPT result '+' indicates positive high-throughput NIPT result 'inc' indicates inconclusive high-throughput NIPT result				
Abbreviations: NIPT, non-invasive prenatal testing; FMH, fetomaternal haemorrhage testing; CB, cord blood				

Model inputs

Summaries of the model inputs are presented below. Further details on the identification of the model inputs and their sources are given, starting on page 98 of the diagnostics assessment report.

Target population characteristics

The annual number of pregnancies in RhD-negative women in England was estimated to be of 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 RhD-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 RhD negative.

The proportion of RhD-positive babies born to women who are RhD positive was estimated as 61.6%. This rate was applied across all pregnancies, that is, the first and later pregnancies.

Test characteristics

The diagnostic accuracy of high-throughput NIPT for fetal RhD status 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 (table 13). These studies were considered the most relevant to NHS clinical practice.

Table 13 Test characteristics

Pooled NIPT accuracy from bivariate synthesis model	Sensitivity (mean, 95% CI)	Specificity (mean, 95% CI)	Proportion of inconclusive results
UK Bristol studies only (treating inconclusive results as if testing positive)	0.998 (0.992–0.999)	0.942 (0.920–0.959)	6.7%
Abbreviation: NIPT, non-invasive prenatal testing.			

Clinical effectiveness of anti-D immunoglobulin

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 14.

Table 14 Clinial effectiveness of RAADP and postpartum anti-D prophylaxis

	Odds ratio: sensitisation with RAADP[1] (95% CI)	Odds ratio: sensitisation at birth, follow-up up to 6 months, with postpartum anti-D prophylaxis[2] (95% CI)	Sensitisation rate without RAADP[1] (95% CI)	Sensitisation rate with RAADP (95% CI)	Sensitisation rate without RAADP and without postpartum anti-D prophylaxis (95% CI)
NICE TA156 (2009)	0.37 (0.21 to 0.65)	–	0.95 (0.18 to 1.71)	0.35 (0.29 to 0.40)	–
Crowther et al. (1997)	–	0.08 (0.06 to 0.11)	0.95[3] (0.18 to 1.71)	–	10.7 (8.0 to 13.8)
[1] Versus no RAADP, conditional on having postpartum anti-D prophylaxis [2] Versus no postpartum anti-D prophylaxis, conditional on no RAADP [3] Baseline-sensitisation rate of no RAADP assumed the same					
Abbreviations: CI, confidence interval; RAADP, routine antenatal anti-D prophylaxis.					

Adherence

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% events (before 20 weeks' gestation events), it was assumed that women had the minimum required dose of 250 IU anti-D immunoglobulin.

The National Comparative Audit of Blood Transfusion: 2013 Audit of anti-D immunoglobulin prophylaxis 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%). Also, the audit showed that a very high proportion

of eligible women (98.4%) had postpartum anti-D prophylaxis. For documented potentially sensitising events, it showed that about 96% of eligible women having these events had anti-D immunoglobulin. Within the economic model, it was assumed that compliance with RAADP was 99.0% and that compliance with postpartum anti-D prophylaxis was 98.4%.

There was limited evidence on adherence to NIPT for fetal RhD status, so it was assumed that the use of NIPT has no additional effect on adherence.

Effects of sensitisations

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

For the base-case analysis, the cost of high-throughput NIPT per sample was estimated to be [redacted], taking into account consumables, staffing, equipment, and indirect and overhead costs. This is the estimated cost of testing at full capacity that is, dealing with at least 100,000 samples. An estimated royalty payment of [redacted] of the test cost was assumed to be added to the unit cost of the test, bringing the base-case estimate of the cost of the test to [redacted]. 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.

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-, 1500- and 2500-unit vials) are available. Weighted averages based on recommended dose regimens and market share were calculated. The cost of anti-D immunoglobulin for potentially sensitising events was estimated to be

£31.69. The cost of RAADP was estimated to be £41.58. The cost of postpartum anti-D prophylaxis was estimated to be £35.69. The cost of anti-D immunoglobulin administration was set to £5.

Currently, cord blood typing should be done to confirm the baby's RhD status and maternal blood samples should be 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 was estimated to be £128.10 (for testing by flow cytometry, and NHS Blood and Transport Red Cell Immunohaemotology).

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 sourced from the NHS reference costs 2014–15. This resulted in an estimated total average 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 on routine antenatal anti-D prophylaxis for women who are rhesus D negative (updated to 2015 prices).

Health-related quality of life

The health-related quality-of-life utilities relating to minor and major developmental problems were assumed to be the same as those used in the NICE technology appraisal guidance on routine antenatal anti-D prophylaxis for women who are rhesus D negative (table 15).

Table 15 Utilities

	Mean	Standard error
Utility for general population	0.88	0.02
Utility for minor development problems	0.85	0.02
Utility for major development problems	0.42	0.03

Base-case results

The following assumptions were applied in the base-case analysis:

- 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 RhD-negative women is based on the white British population
- the proportion of RhD-positive babies born to RhD-negative women is assumed to be the same irrespective of pregnancy number
- the probability of having a RhD-positive baby in the general population of Rh-negative women (61.6%) is combined with the diagnostic accuracy results in terms of sensitivity and specificity (where inconclusive results are treated as test positive) to determine the number of RhD-positive babies in the model
- the probability of having a RhD-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 RhD positive or in whom the results are inconclusive
- in women with an inconclusive NIPT result, the existing care pathway is unchanged and they are treated the same as women who test positive in terms of RAADP, and tests and treatment after potentially sensitising events
- women identified to be offered RAADP will have supplementary anti-D immunoglobulin at the minimum dose needed for any potentially sensitising events
- potentially sensitising events that involve fetal death are assumed independent of previous sensitisation within the same pregnancy

- women with false-negative test results but who are provided with cord blood typing and postpartum anti-D prophylaxis are assumed to have a sensitisation rate of 0.95%, despite forgoing anti-D immunoglobulin treatment for potentially sensitising events
- 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
- no adverse health effects from using a blood-based product such as anti-D immunoglobulin.

Table 16 presents the base-case results for each postpartum testing scenario compared with current practice of 'no test and RAADP'.

Table 16 Base-case results – costs, QALYs and ICERs

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 (PP1) versus no test and RAADP	£15,400,187	2,433,756	−£583,538	−0.46	£1,269,050
Postpartum scenario 2 (PP2) versus no test and RAADP	£15,312,630	2,433,737	−£671,095	−19.13	£35,087
Postpartum scenario 3 (PP3) versus no test and RAADP	£15,498,942	2,433,756	−£484,783	−0.46	£1,054,281
Postpartum scenario 4 (PP4) versus no test and RAADP	£15,410,610	2,433,737	−£573,114	−19.13	£29,964

PP1: postpartum cord blood typing and fetomaternal haemorrhage testing would continue to be done, based current guidelines, in all women regardless of the fetal RhD status identified through high-throughput NIPT.

PP2: postpartum cord blood typing, fetomaternal haemorrhage testing (and by implication postpartum anti-D prophylaxis) would be withheld if high-throughput NIPT of fetal RhD status identifies a RhD-negative fetus, but would continue to be done if high-throughput NIPT was inconclusive or had identified a RhD-positive fetus.

PP3: postpartum cord blood typing would be done if high-throughput NIPT of fetal RhD status identifies a RhD-negative fetus. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis would be administered if high-throughput NIPT was inconclusive or identifies a RhD-positive fetus.

PP4: postpartum cord blood typing would not be done in any women. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis administered if high-throughput NIPT was inconclusive or had identified a RhD-positive fetus.

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

All NIPT strategies are less costly and less effective than current practice (no test and RAADP). Net health benefits were also calculated using maximum acceptable ICERs of £20,000 and £30,000 (table 17). The strategy with the highest net health benefit is the most cost-effective strategy. Results show that all NIPT strategies have greater net health benefit than current practice.

Table 17 Base-case results – net health benefits

Strategies	**Population NHB (maximum acceptable ICER=£20,000)**	**Population NHB (maximum acceptable ICER=£30,000)**
No test and RAADP (current clinical practice)	2,432,957	2,433,223
Postpartum scenario 1 (PP1) versus No test and RAADP	2,432,986	2,433,242
Postpartum scenario 2 (PP2) versus no test and RAADP	2,432,972	2,433,227
Postpartum scenario 3 (PP3) versus no test and RAADP	2,432,981	2,433,239
Postpartum scenario 4 (PP4) versus no test and RAADP	2,432,967	2,433,223
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 status identified through high-throughput NIPT. PP2: postpartum cord blood typing, fetomaternal haemorrhage testing (and by implication postpartum anti-D prophylaxis) would be withheld if high-throughput NIPT of fetal RhD status identifies a RhD-negative fetus, but would continue to be done if high-throughput NIPT was inconclusive or had identified a RhD-positive fetus. PP3: postpartum cord blood typing would be done if high-throughput NIPT of fetal RhD status identifies a RhD-negative fetus. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis would be administered if high-throughput NIPT was inconclusive or identifies a RhD-positive fetus. PP4: postpartum cord blood typing would not be done in any women. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis administered if high-throughput NIPT was inconclusive or had identified a RhD-positive fetus.		
Abbreviations: ICER, incremental cost-effectiveness ratio; NIPT, non-invasive prenatal testing; RAADP, routine antenatal anti-D prophylaxis.		

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 an RhD-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.

The differences in costs between the different strategies are mainly driven by different postpartum testing costs and postpartum anti-D prophylaxis costs (table 18). In terms of postpartum testing and treatment, relative to current practice:

- PP1 is almost equivalent to current practice.
- PP2 decreases postpartum care costs by avoiding cord blood typing for women who test negative on NIPT; but there is an increased cost of managing sensitisations because women with false-negatives results are not picked up at delivery so do not have postpartum anti-D prophylaxis.
- PP3 increases postpartum care costs because, although cord blood typing is avoided for those who test positive on NIPT, this results in unnecessary fetomaternal haemorrhage tests and postpartum anti-D prophylaxis in women with false-positive tests (which includes those who test inconclusive but carry an RhD-negative baby).
- PP4 decreases postpartum care costs by avoiding cord blood typing for all women.

The added cost of managing sensitisations and their associated health consequences in later pregnancies is largest for the strategies with more sensitisations (PP2 and PP4), and is very small for strategies PP1 and PP3 (about £2,000 per 100,000 pregnancies).

Table 18 Breakdown of incremental costs

Cost item	NIPT PP1	NIPT PP2	NIPT PP3	NIPT PP4
NIPT cost	£1,585,117	£1,584,861	£1,585,117	£1,584,861
PSE management costs	−£626,165	−£627,470	−£626,165	−£627,470
RAADP costs	−£1,544,149	−£1,544,887	−£1,544,149	−£1,544,887
Postpartum test and anti-D costs	−£43	−£152,771	£98,712	−£54,790
Sensitisation costs	£1,703	£69,173	£1,703	£69,173
Total incremental cost	−£583,538	−£671,095	−£484,783	−£573,114

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 status identified through high-throughput NIPT.

PP2: postpartum cord blood typing, fetomaternal haemorrhage testing (and by implication postpartum anti-D prophylaxis) would be withheld if high-throughput NIPT of fetal RhD status identifies a RhD-negative fetus, but would continue to be done if high-throughput NIPT was inconclusive or had identified a RhD-positive fetus.

PP3: postpartum cord blood typing would be done if high-throughput NIPT of fetal RhD status identifies a RhD-negative fetus. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis would be administered if high-throughput NIPT was inconclusive or identifies a RhD-positive fetus.

PP4: postpartum cord blood typing would not be done in any women. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis administered if high-throughput NIPT was inconclusive or had identified a RhD-positive fetus.

Abbreviation: NIPT, non-invasive prenatal testing; PSE, potentially sensitising event.

Table 19 presents a fully incremental analysis of NIPT for fetal RhD status for the different postpartum testing strategies. In this analysis, strategy PP4 is dominated by strategy PP2 because it has the same number of QALYs but is more expensive than PP2. Strategy PP3 is dominated by strategy PP1 because it has the same number of QALYs but is more expensive than PP1.

Table 19 Fully incremental cost effectiveness results

Strategies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£ saved /QALY lost)
NIPT PP2	£15,312,630	2,433,737	–	–	–
NIPT PP1	£15,400,187	2,433,756[1]	£87,557	18.67	£4,690
No test and RAADP	£15,983,725	2,433,756[1]	£583,538	0.46	£1,269,050
NIPT PP4	£15,410,610	2,433,737	–	–	Dominated
NIPT PP3	£15,498,942	2,433,756	–	–	Dominated

[1] Total QALYs for NIPT PP1 is 2,433,755.81 and for NIPT PP1 is 2,433,756.27

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 status identified through high-throughput NIPT.

PP2: postpartum cord blood typing, fetomaternal haemorrhage testing (and by implication postpartum anti-D prophylaxis) would be withheld if high-throughput NIPT of fetal RhD status identifies a RhD-negative fetus, but would continue to be done if high-throughput NIPT was inconclusive or had identified a RhD-positive fetus.

PP3: postpartum cord blood typing would be done if high-throughput NIPT of fetal RhD status identifies a RhD-negative fetus. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis would be administered if high-throughput NIPT was inconclusive or identifies a RhD-positive fetus.

PP4: postpartum cord blood typing would not be done in any women. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis administered if high-throughput NIPT was inconclusive or had

Abbreviation: ICER, incremental cost-effectiveness ratio; NIPT, non-invasive prenatal testing; QALY, quality-adjusted life year; RAADP, routine antenatal anti-D prophylaxis.

The cost-effectiveness acceptability curve shows that the highest probability of being cost-effective is obtained by PP1 with 0.65 and 0.73 for maximum acceptable ICER values of £20,000 and £30,000 respectively. For the same maximum acceptable ICER values, the probability of PP2 being cost-effective is 0.30 and 0.22 respectively.

Sensitivity analyses

Sensitivity analyses were carried out on the following model inputs:

- diagnostic accuracy of NIPT for fetal RhD status
- using NIPT at different gestational periods
- rate of inconclusive NIPT results
- clinical effectiveness of RAADP
- adherence to RAADP and postpartum anti-D prophylaxis
- cost of anti-D immunoglobulin and NIPT
- anti-D immunoglobulin administration regimen.

An additional postpartum testing strategy was evaluated, in which postpartum cord blood typing would be done if high-throughput NIPT of fetal RhD status identified an RhD-negative fetus or if the test result was inconclusive. Fetomaternal haemorrhage testing and postpartum anti-D prophylaxis would be administered if a RhD-positive fetus was identified either by a positive NIPT result or by cord blood typing in the inconclusive test result group.

The sensitivity analyses show that the results 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. Full results of the sensitivity analyses can be found starting on page 125 of the diagnostics assessment report.

Sensitivity analysis on diagnostic accuracy

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

Sensitivity analysis on inconclusive results

Because inconclusive results are treated as positive results, a higher rate of inconclusive results increases the number of false positives. In the sensitivity analysis on the rates of inconclusive results, net health benefits of NIPT strategies fell as the rate of inconclusive results increased, but the net health benefits of PP1 and PP3 did not fall below the net health benefits of current practice. When the rate of inconclusive results was low, PP3 offered higher net health benefit than PP1. This is because the amount of unnecessary postpartum fetomaternal haemorrhage testing and postpartum anti-D prophylaxis was reduced when the number of false-positive results fell. When the rate of inconclusive results was high, PP1 offered the highest net health benefit.

Sensitivity analysis on test and treatment costs

The unit cost of an NIPT is subject to uncertainty because it depends on throughput (the annual total number of samples) and the level of the royalty fee. Also, introducing NIPT may impose additional costs in routine antenatal care in terms of appointments and staff time. 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 offering higher net health benefit than NIPT strategies. For example, raising the cost for each high-throughput NIPT to £24.64 would result in current practice offering highest net health benefits.

Sensitivity analysis on the cost of fetomaternal haemorrhage testing

Reducing the cost of 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 offered less net health benefits compared with current practice, while PP1 and PP3 had greater net health benefits compared with current practice.

Sensitivity analysis on an alternative postpartum testing strategy

An alternative postpartum testing strategy was assessed, which separated women in whom NIPT predicted a RhD positive fetus from women in whom NIPT gave an inconclusive result (and were therefore treated as if the fetus was RhD positive). This involved cord blood typing for women identified as having an RhD-negative fetus by NIPT and for women who had an inconclusive NIPT result, but not doing cord blood typing for women in whom NIPT indicated an RhD-positive fetus. This 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 postpartum testing strategy compared with current practice was £1,638,356 saved per QALY lost.

3 Summary of the main findings from the assessment

Clinical effectiveness

Eight studies were included in the diagnostic accuracy review of high-throughput NIPT testing for fetal RhD status. Of these, 3 studies were based in Bristol (UK). Most of the included studies were judged to be at low risk of bias.

Meta-analyses showed very high diagnostic accuracy of high-throughput NIPT for fetal RhD status. In the primary analyses, in which women with

inconclusive test results were treated as having an RhD positive fetus, the summary false-negative rate (that is, women at risk of sensitisation) was 0.34% (95% CI 0.15 to 0.76) and the summary false-positive rate (that is, women needlessly having RAADP) was 3.86% (95% CI 2.54 to 5.82). A subgroup analysis of the 3 studies based in Bristol (UK) showed a slightly lower false-negative rate of 0.21% (95% CI 0.09 to 0.48), and a higher false-positive rate of 5.73% (95% CI 4.58 to 7.16). The false-positive rate was mostly because of treating the 6.9% of women (from the Bristol studies) who had an inconclusive test result as if they had a positive test result.

The diagnostic accuracy of high-throughput NIPT differed by gestational age. The data suggested that high-throughput NIPT is consistently accurate at any time after 11 weeks' gestation.

All 7 studies included in the clinical effectiveness review were judged to be at high risk of bias. All, except one study, were done in non-UK countries, and so the generalisability of their findings to clinical practice in the NHS was limited because of variations in national guidelines and health policies between countries.

Uptake rates of NIPT for fetal RhD status ranged from 70% to more than 95% (7 studies). Uptake rates of RAADP in women who accepted NIPT for fetal RhD status and had a positive result ranged from 86% to 96.1% (4 studies). Uptake rates of postpartum anti-D prophylaxis in women who accepted NIPT for fetal RhD status and had a positive result ranged from 92% to 99.7% (3 studies).

Three non-comparative studies evaluated changes in anti-D immunoglobulin use after NIPT for fetal RhD status was implemented. All found that testing reduced the total use of anti-D immunoglobulin.

Results from the simulation study suggested that using NIPT for fetal RhD status would substantially reduce the number of women having RAADP unnecessarily, from 38.9% to 5.7%. Results also showed that NIPT for fetal

RhD status could increase sensitisation rates by 3 sensitisations per 100,000 women if postpartum cord blood typing is continued, or 13 per 100,000 women if postpartum anti-D prophylaxis is given based on the NIPT result. This is based on the assumption that women who do not have NIPT for fetal RhD status are still offered RAADP.

Costs and cost effectiveness

The review of existing cost-effectiveness studies identified 7 relevant studies. Conflicting results were found across the existing studies, with 3 studies reporting that NIPT for fetal RhD status did not appear cost effective. The unit cost of the test was identified as a key driver of the cost-effectiveness results.

The de novo economic model indicated that using high-throughput NIPT for fetal RhD status to guide anti-D immunoglobulin prophylaxis was cost saving compared with the current practice of providing RAADP to all women who are RhD negative. The size of the cost saving appears to be highly sensitive to the cost of the test.

Four postpartum testing scenarios were all found to be cost saving but less effective compared with current practice. Cost savings varied between about £485,000 and £671,000 per 100,000 pregnancies. QALY losses varied between 0.5 QALYs and 19.1 QALYs per 100,000 pregnancies.

In the base-case analysis, the strategy that had the highest net health benefit and the highest probability of being cost-effective for maximum acceptable ICER values of £20,000 and £30,000 per QALY was the one in which the NIPT result is used to guide RAADP only, and all women have postpartum cord blood typing to guide fetomaternal haemorrhage testing and postpartum anti-D prophylaxis (PP1). But, the most efficient postpartum strategy varied depending on the estimates of diagnostic accuracy and the rate of inconclusive results.

A postpartum strategy that distinguishes between inconclusive NIPT results and positive NIPT results offered the greatest cost savings in the economic

model. In this strategy, women in whom NIPT indicated an RhD-negative fetus or was inconclusive would have postpartum cord blood typing to guide using fetomaternal haemorrhage testing and postpartum anti-D prophylaxis, but fetomaternal haemorrhage testing and postpartum anti-D prophylaxis would be provided without cord blood typing for women in whom NIPT indicated an RhD positive fetus.

4 Issues for consideration

Diagnostic accuracy and clinical effectiveness

The findings from this assessment showed high diagnostic accuracy of high-throughput NIPT for fetal RhD status. The results suggest that NIPT is sufficiently accurate for determining fetal RhD status after 11 weeks' gestation. Sensitivity analyses on the accuracy of NIPT and on the timing of testing between 11 and 23 weeks did not materially alter the cost-effectiveness results.

Based on the analysis of studies set in Bristol, UK, about 7% of women would have an inconclusive NIPT result, be treated as having an RhD-positive fetus and be offered RAADP.

Introduction of NIPT for fetal RhD status would result in between 3 and 13 additional sensitisations per 100,000 women, depending on the postpartum testing strategy. These extra sensitisations would have a minimal effect on fetal mortality in later pregnancies, with an estimated maximum of 5 extra deaths per 1 million pregnancies.

Cost effectiveness

In the economic model, all high-throughput NIPT strategies result in increased numbers of sensitisations, and therefore QALY losses, compared with current practice. Resulting QALY losses were relatively small, ranging from 0.5 QALYs to 19.1 QALYs lost per 100,000 pregnancies. QALY losses were smallest when postpartum cord blood typing followed by fetomaternal haemorrhage testing and postpartum anti-D prophylaxis was done in women

in whom NIPT had identified an RhD-negative fetus (PP3) or performed in all women (PP1). This ensures that if any false-negative results are identified, these women can then be offered postpartum anti-D prophylaxis, therefore reducing the number of sensitisations compared with a scenario in which these women did not have cord blood typing.

The results of the cost-effectiveness model were sensitive to both the cost of the high-throughput NIPT for fetal RhD status and the cost of anti-D immunoglobulin. The cost of NIPT would need to stay below £24.64 for high-throughput NIPT to be considered cost-effective compared with current practice. For the base case analysis the cost of high-throughput NIPT per sample was estimated to be [redacted]. This is the estimated cost of testing at full capacity that is, testing at least 100,000 samples per year. An estimated royalty payment of [redacted] of the test cost was added to the unit cost of the test, bringing the base case estimate of the test cost to [redacted]. But, the unit cost of NIPT depends on the expected annual throughput of samples and the level of the royalty fee. The International Blood Group Reference Laboratory provided a range of expected unit costs for NIPT for use in the assessment ([redacted] to [redacted], not including a royalty fee).

There are potential benefits of high-throughput NIPT for fetal RhD status, which have not been captured in the economic model. For example, the ethical issues associated with unnecessarily giving a blood-based product. Also, although anti-D immunoglobulin is considered safe, there is still uncertainty about the potential risk associated with prion disease or other unknown pathogens.

In most analyses, a postpartum test strategy of cord blood typing for all women, followed by fetomaternal haemorrhage testing and postpartum anti-D prophylaxis if indicated (PP1), is the most cost-effective strategy.

Sensitivity analyses showed that when the rate of inconclusive results is low, the most cost-effective postpartum test strategy was cord blood typing followed by fetomaternal haemorrhage testing and postpartum anti-D

prophylaxis if NIPT had identified an RhD-negative fetus, and fetomaternal haemorrhage testing and postpartum anti-D prophylaxis (without cord blood typing) if NIPT was inconclusive or had identified an RhD-positive fetus (PP3). When the rate of inconclusive test results is high, the preferred postpartum test strategy is cord blood typing for all women, followed by fetomaternal haemorrhage testing and postpartum anti-D prophylaxis where indicated (PP1).

A fifth postpartum testing strategy was examined by the external assessment group in which cord blood typing would be done in women identified by NIPT as having an RhD-negative fetus and in women who had an inconclusive NIPT result to guide fetomaternal haemorrhage testing and postpartum anti-D prophylaxis, but cord blood typing would not be done in women in whom the NIPT indicated an RhD-positive fetus. This strategy dominated all other test strategies.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Women who are from black, Asian and minority ethnic groups are more likely to have less accurate results with NIPT for fetal RhD status. For example, in women of African family origin, because of the presence of RHD-pseudogene, prenatal detection of fetal RhD type from maternal blood would lead to higher rates of false-positive results in this particular population. This population would be offered anti-D immunoglobulin even though the baby is RhD negative, in line with the current standard of care. So, fetal wellbeing and maternal care would not be affected and would not differ between ethnic groups.

6 Implementation

Twelve studies were identified in a review of implementation of NIPT for fetal RhD status. Most studies reported that NIPT of fetal RhD status was feasible and should be recommended. Several studies reported potential issues relating to implementation, such as programme anti-D prophylaxis adherence. Some studies highlighted the importance of short transport times for samples and effective management of transporting samples. Some studies also identified the need for greater knowledge of NIPT among physicians and midwives.

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 rhesus blood groups and anti-D treatment was limited, which could be a barrier to implementation.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

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

- Yang H, Goncalves P, Llewellyn A, Griffin S, Walker R, Harden M, Palmer S, Simmonds M. 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. *Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence.* May: 2016.

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

I. Provider of technology included in the final scope:

- International Blood Group Reference Laboratory

II. Other commercial organisations:

- CSL Behring UK Ltd

III. Professional groups and patient/carer groups:

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

IV. Research groups:

- None

V. Associated guideline groups:

- None

VI. Others:

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

Appendix B: Glossary of terms

Anti-D immunoglobulin

A treatment given to RhD-negative pregnant women to prevent sensitisation

Cell-free fetal DNA

Fetal DNA circulating freely in the maternal bloodstream

Fetomaternal haemorrhage

An event that occurs when the membranous barrier between the maternal and fetal circulation stops working and fetal cells enter the maternal blood

Fetomaternal haemorrhage test

Also known as the Kleihauer test; this 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 in which antibodies in a pregnant woman's blood destroy their baby's blood cells

Potentially sensitising event

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

RHD pseudogene

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

Sensitisation

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