ERRATUM TO

Technology Assessment Report for NICE: 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

An overall update of the original report' results due to (i) a correction on the general population probability of having a Rhesus positive baby to 61.6% (from an erroneous mean value of 65.9%); and (ii) a correction on the proportion of RhD-positive babies in RhD-negative women testing inconclusive, updated from 69.7% to 70.1%.

1. Page 20-21: The range of cost savings across the post-partum strategies has been corrected. The estimated increase in the cost of the test to alter the base case conclusions has been correct to [redacted].

   Corrected pages 20-21 are copied below.

2. Page 101: The proportions of inconclusive NIPT results (of UK and diagnostic studies) used in the model have been corrected.

   A corrected page 101 is copied below.

3. Page 110: Two further economic model assumptions have been added to the list of assumptions relating to the probability of having an RhD-positive baby.

   A corrected page 110 is copied below.

4. Page 111-113: NIPT inconclusive results reported on Table 23 have been corrected.

   Corrected pages 111-113 are copied below.

5. Pages 116-117: The numbering of the sensitivity analysis has been corrected.

   Corrected pages 116-117 are copied below.

6. Page 119: The estimated QALY loss per additional sensitisation has been corrected. Base case incremental cost-effectiveness results reported on Table 26 have been corrected. Base case results reported in the cost-effectiveness plane in Figure 13 have been corrected.

   Corrected pages 119-121 are copied below.

7. Pages 122-123: The breakdown of estimated incremental costs over the different NIPT strategies compared to current practice reported on Table 27 has been corrected. Additionally, the results reported in the following paragraph interpreting this breakdown have been corrected.

   Corrected pages 122-123 are copied below.

8. Pages 124-125: Base case fully incremental cost-effectiveness results reported on Table 28 have been corrected. The results reported in the following paragraph interpreting the fully incremental outcomes have been corrected. The cost-effectiveness acceptability curves reported in Figure 14 have been corrected.

   Corrected pages 124-125 are copied below.

9. Page 126-127: Incremental cost-effectiveness results for the sensitivity analysis on NIPT accuracy evidence reported on Table 29 have been corrected.

   Corrected pages 126-127 are copied below.

10. Page128: Incremental cost-effectiveness results for the sensitivity analysis on the timing of the NIPT reported on Table 30 have been corrected. The results reported in the following paragraph interpreting the sensitivity analysis outcomes have been corrected.

    A corrected page 128 is copied below.

11. Page 129: Incremental cost-effectiveness results for the sensitivity analysis on the effectiveness of RAADP reported on Table 31 have been corrected.

    A corrected page 129 is copied below.

12. Page 130: Incremental cost-effectiveness results for the sensitivity analysis on the uptake rates of RAADP and post-partum anti-D immunoglobulin reported on Table 32 have been corrected.

    A corrected page 130 is copied below.

13. Page 132-135: The cost-effectiveness outcomes reported on Figure 16 and Figure 17 for the sensitivity analysis on the rate of NIPT inconclusive results have been corrected. Additionally, the cost-effectiveness results of the two-way sensitivity analysis on the cost of NIPT and anti-D showed in Figure 18 have been corrected, together with the results reported in section 6.5.2.6. Incremental cost-effectiveness results for the sensitivity analysis on the fetal-maternal haemorrhage test cost reported on Table 33 have been corrected.

    Corrected pages 132-135 are copied below.

14. Page 136-139: The cost-effectiveness results for the sensitivity analysis on the post-partum management of inconclusive results reported on section 6.4.2.8 have been corrected. Additionally, the summary of base case and key sensitivity analysis results shown on Table 34 has been corrected. Figures reported in the discussion and conclusion sections have been corrected.

    Corrected pages 136-139 are copied below.

15. Page 141-143: The estimated additional cost of high-throughput NIPT above that modelled in the base case in order for No test and RAADP to be the preferred strategy has been corrected.

    Corrected pages 141-143 are copied below.

16. Page 144-145: The estimated additional cost of high-throughput NIPT above that modelled in the base case in order for No test and RAADP to be the preferred strategy has been corrected.

    Corrected pages 144-145 are copied below.

PAGES 20-21:

Three non-comparative studies reported on reduction in administration of anti-D. All suggested that anti-D administration was largely avoided in women with an RhD negative fetus. A pilot study 3 in England found that around 35% of women who received NIPT avoided unnecessary anti-D administration.

The compliance rate with antenatal anti-D prophylaxis ranged from 86% to 96.1% (four studies), and compliance rates with postpartum anti-D ranged from 92% to 99.7% (three studies) in women who undertook NIPT and received a positive result. High-throughput NIPT testing uptake rates ranged from 70% to over 95% (seven studies). None of the included studies reported data on adverse events associated with NIPT.

The results from the simulation study suggested that use of NIPT testing to determine antenatal anti-D use would substantially reduce the number of women receiving anti-D unnecessarily, from 38.9% to 5.7%, consistent with evidence identified by the review. The use of NIPT would cause an extra 3 sensitisations per 100,000 women if cord blood testing is continued (at least in women with a negative NIPT test result) as the basis for administering postpartum anti-D. If cord blood testing is withdrawn (except for women who did not receive an NIPT test, or who had an inconclusive test result) and the NIPT test used to decide on postpartum anti-D administration then there would be an extra 13 sensitisations per 100,000 women. These additional sensitisations are few compared to the underlying rate of sensitisation with antenatal anti-D (280 per 100,000 women). Sensitisation rates could be higher if women who do not receive an NIPT test are also less likely to receive antenatal anti-D. These results suggest that cord blood testing could potentially be withdrawn, and NIPT test results (if available and conclusive) may be used to prescribe postpartum anti-D. This conclusion will partly depend on whether the extra 10 sensitisations per 100,000 RhD negative women caused by withdrawing cord blood testing can be considered an ethically acceptable increase.

1.4.3 Evidence on implementation

Twelve studies were included in the review of implementation. Most of the included studies were large cohort studies reporting implementation data alongside with diagnostic accuracy data, while one study was a survey based in the UK (London). All the cohort studies suggested that high throughput RhD genotyping of foetuses in all RhD negative women was feasible. A number of studies reported potential issues of implementation such as those relating to programme anti-D prophylaxis compliance. The UK survey study13 revealed that

women's current knowledge of Rhesus blood groups and anti-D administration was found to be limited, which could be an issue to implementation.

1.4.4 Cost-effectiveness

The *de-novo* health economic model suggests that high-throughput NIPT appears cost saving but also less effective than current practice, irrespective of the post-partum scenario evaluated. However, the magnitude of the potential cost-savings appears sufficient to outweigh the small increase in sensitisations and the associated small QALY loss through using NIPT compared to current practice. Based on a cross section of 100,000 pregnancies, the likely magnitude of cost savings ranges between £485,000 and £671,000 across the separate post-partum strategies. In the base-case analysis, the strategy in which the NIPT result is used to guide RAADP only (i.e. all women continue to receive cord serology with fetal-maternal haemorrhage and post-partum anti-D immunoglobulin) had the highest probability of being cost-effective.

The magnitude of the cost saving appears highly sensitive to the cost of the NIPT itself to the NHS, which comprises the base unit cost per test, the level of any royalty fee, and any increase in antenatal care costs required to accommodate an additional test. A small increase in the cost assumed of [redacted] or more per test would alter these conclusions.

Our findings indicate that the timing of the test does not appear influential in determining the cost-effectiveness results either in terms of diagnostic accuracy or in terms of the extent of management costs for potentially sensitising events that can be avoided. Another important consideration is the rate of high-throughput NIPT inconclusive results. Our findings demonstrate that even with a high-throughput NIPT inconclusive result rate close to 15%, the introduction of NIPT appears to compare favourably to current practice.

1.5 Discussion

1.5.1 Strengths, limitations and uncertainties

A comprehensive literature search was undertaken to identify both published and unpublished studies. Appropriate synthesis methods were employed by taking into account the heterogeneity of study characteristics. The bivariate and HSROC models were used for diagnostic accuracy data, which take into account the trade-off between true/false-positives and models between-study heterogeneity.

Non-English-language studies were excluded. Few studies were identified reporting clinical effectiveness data of using high-throughput NIPT testing to detect fetal RhD status in RhD negative women. Results of the simulation study are sensitive to the parameters used, and should be considered to be speculative.

Due to the limited data available on the evaluation of clinical effectiveness, the potential clinical impact of high-throughput NIPT testing on the care pathway remains unclear. No studies compared NIPT testing to universal administration of antenatal anti-D. No studies were identified reporting comparative data relating to patient-related outcomes such as quality of life or anxiety. Whether the diagnostic performance of high-throughput NIPT testing differs between different ethnic groups remains unclear.

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Table 1 High-throughput NIPT RhD diagnostic test performance at multiple time points and for when including and excluding inconclusive test results

NIPT accuracy per gestation age, Chitty et al [1]	Sensitivity (mean, SE)	Specificity (mean, SE)	Distribution
Treating inconclusive results as if testing positive			
Less than 11 weeks	0.9685 (0.0079)	0.9440 (0.0123)	Log-Normal
Between 11 and 13 weeks	0.9983 (0.0023)	0.9525 (0.0114)	Log-Normal
Between 14 and 17 weeks	0.9967 (0.0045)	0.9534 (0.0141)	Log-Normal
Between 18 and 23 weeks	0.9982 (0.0003)	0.9304 (0.0138)	Log-Normal
More than 24 weeks	1.0000 (0.0010)	0.9574 (0.0076)	Log-Normal
Excluding inconclusive results			
Less than 11 weeks	0.9615 (0.0079*)	0.9970 (0.0123*)	Log-Normal
Between 11 and 13 weeks	0.9981 (0.0023*)	0.9884 (0.0114*)	Log-Normal
Between 14 and 17 weeks	0.9963 (0.0045*)	0.9956 (0.0141*)	Log-Normal
Between 18 and 23 weeks	0.9980 (0.0003*)	0.9847 (0.0138*)	Log-Normal
More than 24 weeks	1.000 (0.0010*)	0.9900 (0.0076*)	Log-Normal

* In the absence of information the SEs were assumed the same as in the approach where inconclusive results were treated as positive results.

6.3.4 NIPT inconclusive results

In the UK studies that inform the base case for the decision model the pooled proportion of inconclusive NIPT results was 6.7%. Across all diagnostic studies which report the number of inconclusive results this proportion is lower at 4.0%. The results of the diagnostic accuracy studies suggest that the probability of an RhD-positive baby is higher among women in whom the high-throughput NIPT is inconclusive compared to the probability across all RhD-

negative women – see Section 4.2.2.4. In section 6.3.2 it was estimated that the probability of RhD-negative women having RhD-positive babies in the first and subsequent pregnancies was 61.6%. In the presence of high-throughput NIPT inconclusive results it is estimated that this probability is 70.1%, irrespective of the pregnancy. This probability is slightly reduced (70.7%) if only UK studies are considered. These latter two probabilities are used to estimate the positive predictive value of the NIPT, and in sensitivity analysis around the post-partum management of women with inconclusive NIPT results (SA8).

6.3.5 Effectiveness of Anti-D immunoglobulin

The introduction of the high-throughput NIPT into the care pathway will be used to determine the level of use of anti-D immunoglobulin. Anti-D immunoglobulin affects the rate of sensitisation in women carrying RhD-positive fetuses and carries a potential risk of adverse effects as it is derived from blood products. The costs and consequences of the introduction of high-throughput NIPT are therefore determined by:

- the efficacy of anti-D immunoglobulin in preventing sensitisation, as this determines the health and cost implications for women from whom this incorrectly withheld due to a false negative high-throughput NIPT result; and
- the costs and adverse effects associated with administration of anti-D immunoglobulin.

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6.3.14 Model parameters and main assumptions

The parameters used within the *de-novo* economic model, and their characteristics, as described above, are outlined in

Table 2 Model parameters

Parameter	Mean value	S.E.	Distribution	Source / calculation
Discounting				
Discount rate for utilities	3.5%	---	---	NICE methods guidance [85]
Discount rate for costs	3.5%	---	---	NICE methods guidance [85]
Target population characteristics				
Population of England(a)	54,316,600	---	---	Office for National Statistics - Annual Mid-year Population Estimates, 2014 [86]
Crude birth rate in England: all births per 1,000 population of all ages (b)	12.18	---	---	Office for National Statistics - Births in England and Wales, 2014[73]
Proportion of pregnancies accounted for by Rh-negative women (c) – reiterated from **Error! Reference source not found.**	15.0%	---	---	Hospital Episode Statistics Analysis and Health and Social Care Information Centre, 2013-14 [74]
Number of women requiring treatment	99,225	---	---	Estimate based on information above [=(a*(b/1000)*c)]
Proportion of 1st pregnancies proceeding to next pregnancy	91.4%	---	---	Office for National Statistics - Birth Summary Tables, England and Wales - Characteristics of Mother 2, England and Wales – average over 5 years (2009 to 2013) [87]
Proportion of 2nd pregnancies proceeding to next pregnancy	40.5%	---	---	Office for National Statistics - Birth Summary Tables, England and Wales - Characteristics of Mother 2, England and Wales – average

Parameter	Mean value	S.E.	Distribution	Source / calculation
				over 5 years (2009 to 2013) [87]
Proportion of 3rd pregnancies proceeding to next pregnancy	58.3%	---	---	Office for National Statistics - Birth Summary Tables, England and Wales - Characteristics of Mother 2, England and Wales – average over 5 years (2009 to 2013) [87]
Median time between pregancies (in years)	3.17	---	---	Office for national statistics - Birth Summary Tables, England and Wales 2014 - Characteristics of Mother 2, England and Wales, 2013 [87]
Compliance				
Compliance with RAADP	99.0%	0.1%	Beta	National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21]
Compliance with RAADP if high-throughput NIPT performed	99.0%	0.1%	Beta	Assumed the same as compliance with RAADP
Compliance with post-partum Anti-D immunoglobulin (dose of at least 500 IU given within 3 days of delivery)	98.0%	0.2%	Beta	National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis[21]
High-throughput NIPT inconclusive results				
Proportion of high-throughput NIPT inconclusive results: All studies reporting inconclusive results	6.7%	0.4%	Beta	Diagnostic accuracy review (see section 4 above)
Proportion of high-throughput NIPT inconclusive results: UK Bristol studies	4.0%	0.1%	Beta	Diagnostic accuracy review (see section 4 above)
Proportion of RhD-positive babies in high-throughput NIPT	70.1%	0.7%	Beta	Diagnostic accuracy review (see section 4 above)

Parameter	Mean value	S.E.	Distribution	Source / calculation
inconclusive results: All studies reporting inconclusive results				
Proportion of RhD-positive babies in high-throughput NIPT inconclusive results: UK Bristol studies	70.7%	0.3%	Beta	Diagnostic accuracy review (see section 4 above)
Sensitisation events				
Probability of having at least 1 potentially sensitising event	15.5%	0.5%	Beta	National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21]
Probability of performing a FMH test given at least 1 potentially sensitising event	69.3%	1.4%	Beta	National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21]
Probability of receiving Anti-D after having at least 1 potentially sensitising event	95.8%	0.6%	Beta	National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21]
Probability of women having a miscarriage (including stillbirth and intrauterine death)	4.7%	0.3%	Beta	National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21]
Consequences of sensitisation				
Fetal loss rate per woman at risk	5.0%	1.0%	Beta	Finning et al 2008 [2] and previous NICE assessment (TA 156) [72]
Proportion of babies affected by HDN with minor developmental problems	6.0%	2.0%	Beta	Previous NICE assessment (TA 156) [72]
Duration of minor developmental problems (years)	16	5	Beta	Previous NICE assessment (TA 156) [72]
Proportion of babies affected by HDN with major developmental	5.0%	1.0%	Beta	Finning et al 2008 [2] and previous NICE assessment (TA 156) [72]

Parameter	Mean value	S.E.	Distribution	Source / calculation
problems				
Life expectancy for person with major developmental problems	59.5	Range 40-79	Uniform	Previous NICE assessment (TA 156) [72]
Utilities				
Utility for 'normal' person	0.88	0.02	Beta	Previous NICE assessment (TA 156) [72]
Utility for minor development problems	0.85	0.02	Beta	Previous NICE assessment (TA 156) [72]
Utility for major development problems	0.42	0.03	Beta	Previous NICE assessment (TA 156) [72]
Costs				
Cost of high-throughput NIPT	[redacted]	---	---	Provided by the company – commercial in confidence
Royalty fee of high-throughput NIPT	[redacted]	---	---	Provided by the company – commercial in confidence
Cost of RAADP	£41.58	---	---	BNF [83] and National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21] - weighted average of single- and two-dose anti-D regimen costs and their market share
Cost of potentially sensitising events anti-D immunoglobulin	£31.69	---	---	BNF [83] and National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21] - weighted average of dose anti-D regimen cost and the likelihood of pre and post-20 weeks events
Cost of post-partum anti-D immunoglobulin	£35.69	---	---	BNF [83] and National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21] - weighted average of dose anti-D regimen cost and their market share
Cost of anti-D immunoglobulin	£5.00	£2.00	Gamma	Previous NICE assessment (TA 156) [72]

Parameter	Mean value	S.E.	Distribution	Source / calculation
administration per RhD-negative woman treated				
Cost of post-partum blood cord serology	£4.18	---	---	Szczepura et al [61], updated to 2015
Cost of feto-maternal haemorrhage testing	£128.10	---	---	Provided by clinical experts
Cost of phlebotomy	£3.32	---	---	Szczepura et al [61], updated to 2015 prices
Cost of management of a sensitised woman and sensitised neonate	£3,166.72	£700.00	Gamma	Previous NICE assessment (TA 156) [72]
Yearly cost of minor developmental problems	£110.58	£35.00	Gamma	Previous NICE assessment (TA 156) [72]}, updated to 2015 prices
Yearly cost of major developmental problems	£573.72	£405.73	Gamma	Previous NICE assessment (TA 156) [72], updated to 2015 prices

6.4 Analytic methods

In exploring the alternative means by which the introduction of high-throughput NIPT could impact on the post-partum care pathway, we first present results for each post-partum scenario separately compared with 'no test and RAADP'. Thereafter we combine them and compare them directly in a full incremental analysis.

The decision-analytic model was evaluated using 10,000 Monte Carlo simulations to reflect the joint uncertainty across all of the inputs according to the probability distributions assigned to each, as shown in

Table 2. All results are presented in terms of the average over 10,000 simulations, as these provide an unbiased estimate of the expected model outcomes. The existing model non-linearity means that the deterministic results are not an accurate estimate of the mean costs and QALYs in each strategy. This non-linearity is likely attributable to the model being structured around the specificity

. Costs refer to 2015 prices.

Within the model the following assumptions are consistent with NICE TA 156 [72]:

- sensitisations do not affect the pregnancy in which they occur;
- anti-D immoglobulin used within one pregnancy has no effect in reducing sensitisations during the next pregnancy;
- the proportion of RhD-negative women is based on the Caucasian population given that this group makes up over 90% of the population of England and Wales;

Furthermore, the following assumptions were made:

- the proportion of RhD-positive babies in Rh-negative women is assumed 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 Rh-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 estimates
- all NIPT are assumed to be performed early enough to determine the use of RAADP at 28 weeks' gestation;
- routine and prophylactic anti-D immunoglobulin 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 we assume that the existing care pathway is unchanged and that they are treated the same as women who test positive in terms of RAADP, anti-D immunoglobulin and associated tests;
- women identified to receive RAADP will receive supplementary anti-D immunoglobulin at the minimum dose required for any potentially sensitising events;
- potentially sensitising events that involve fetal death were assumed independent of previous sensitisation within the same pregnancy;
- women with false negative test results but who are provided with cord serology and post-partum anti-D immunoglobulin are assumed to have a sensitisation rate of 0.95% despite forgoing anti-D immunoglobulin treatment for potentially sensitising events;
- compliance with RAADP is assumed the same with and without NIPT; similarly, compliance for post-partum anti-D immunoglobulin is assumed the same with or without NIPT;

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Table 2 Model parameters

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Discounting				
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Target population characteristics				
Population of England(a)	54,316,600	---	---	Office for National Statistics - Annual Mid-year Population Estimates, 2014 [86]
Crude birth rate in England: all births per 1,000 population of all ages (b)	12.18	---	---	Office for National Statistics - Births in England and Wales, 2014[73]
Proportion of pregnancies accounted for by Rh-negative women (c) – reiterated from **Error! Reference source not found.**	15.0%	---	---	Hospital Episode Statistics Analysis and Health and Social Care Information Centre, 2013-14 [74]
Number of women requiring treatment	99,225	---	---	Estimate based on information above [=(a*(b/1000)*c)]
Proportion of 1st pregnancies proceeding to next pregnancy	91.4%	---	---	Office for National Statistics - Birth Summary Tables, England and Wales - Characteristics of Mother 2, England and Wales – average over 5 years (2009 to 2013) [87]
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				over 5 years (2009 to 2013) [87]
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High-throughput NIPT inconclusive results				
Proportion of high-throughput NIPT inconclusive results: All studies reporting inconclusive results	6.7%	0.4%	Beta	Diagnostic accuracy review (see section 4 above)
Proportion of high-throughput NIPT inconclusive results: UK Bristol studies	4.0%	0.1%	Beta	Diagnostic accuracy review (see section 4 above)
Proportion of RhD-positive babies in high-throughput NIPT inconclusive results: All studies reporting inconclusive results	70.1%	0.7%	Beta	Diagnostic accuracy review (see section 4 above)
Proportion of RhD-positive babies in high-	70.7%	0.3%	Beta	Diagnostic accuracy review (see section 4 above)

Parameter	Mean value	S.E.	Distribution	Source / calculation
throughput NIPT inconclusive results: UK Bristol studies				
Sensitisation events				
Probability of having at least 1 potentially sensitising event	15.5%	0.5%	Beta	National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21]
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Proportion of babies affected by HDN with minor developmental problems	6.0%	2.0%	Beta	Previous NICE assessment (TA 156) [72]
Duration of minor developmental problems (years)	16	5	Beta	Previous NICE assessment (TA 156) [72]
Proportion of babies affected by HDN with major developmental problems	5.0%	1.0%	Beta	Finning et al 2008 [2] and previous NICE assessment (TA 156) [72]
Life expectancy for person with major developmental problems	59.5	Range 40-79	Uniform	Previous NICE assessment (TA 156) [72]

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Utility for 'normal' person	0.88	0.02	Beta	Previous NICE assessment (TA 156) [72]
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Costs				
Cost of high-throughput NIPT	[redacted]	---	---	Provided by the company – commercial in confidence
Royalty fee of high-throughput NIPT	[redacted]	---	---	Provided by the company – commercial in confidence
Cost of RAADP	£41.58	---	---	BNF [83] and National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21] - weighted average of single- and two-dose anti-D regimen costs and their market share
Cost of potentially sensitising events anti-D immunoglobulin	£31.69	---	---	BNF [83] and National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21] - weighted average of dose anti-D regimen cost and the likelihood of pre and post-20 weeks events
Cost of post-partum anti-D immunoglobulin	£35.69	---	---	BNF [83] and National Comparative Audit of Blood Transfusion - 2013 Audit of Anti-D Immunoglobulin Prophylaxis [21] - weighted average of dose anti-D regimen cost and their market share
Cost of anti-D immunoglobulin administration per RhD-negative woman treated	£5.00	£2.00	Gamma	Previous NICE assessment (TA 156) [72]
Cost of post-partum blood cord serology	£4.18	---	---	Szczepura et al [61], updated to 2015

Parameter	Mean value	S.E.	Distribution	Source / calculation
Cost of feto-maternal haemorrhage testing	£128.10	---	---	Provided by clinical experts
Cost of phlebotomy	£3.32	---	---	Szczepura et al [61], updated to 2015 prices
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SA1. We explored alternative sources for the diagnostic performance of high-throughput NIPT. The base case analysis utilises the results from the UK (Bristol) studies, as these are thought to be most generalisable to a UK setting. We also show the results utilising all available studies, regardless of geography. For lower estimates of sensitivity, high-throughput NIPT is expected to result in more false negative results, which are associated with adverse health consequences in terms of additional sensitisations. For lower estimates of specificity, high-throughput NIPT is expected to result in more false positive results, which reduce the amount of unnecessary anti-D immunoglobulin and associated management costs that is avoided;

SA2. We explored the use of high-throughput NIPT at different gestation periods. Performance results from a recent UK study 1 were used to assess the cost and consequences of introducing high-throughput NIPT at 11 to 13 weeks, 14 to 17 weeks and 18 to 23 weeks. Note that the economic model does not incorporate the timing of a potentially sensitising event, and so a threshold analysis is performed to determine the percentage of these costs that would have to occur prior to the NIPT test in order for the ICER to cross a threshold of £20,000 per QALY;

SA3. The base case analysis utilised the same rate of sensitisation with 'no test and RAADP' as was used in the NICE TA 156 [72]. Subsequent to NICE TA 156 a further meta-analysis was performed by Turner et al [79], which suggests that anti-D immunoglobulin could be marginally more effective if all studies are taken into account, reducing the rate of sensitisation with 'no test and RAADP' from 0.35% to 0.30%. The increased efficacy of RAADP will increase the health costs associated with false negative results of high-throughput NIPT, as women will have incorrectly forgone a more effective treatment;

SA4. We explore the impact of an overall change in uptake of anti-D immunoglobulin. Lower uptake of RAADP will reduce the cost savings possible from avoiding unnecessary RAADP, but will also affect the health consequences of additional sensitisations. However, we did not explore an effect of high-throughput NIPT on uptake. The base case analysis assumes that the introduction of the high-throughput NIPT will not alter the proportion of women who comply with anti-D immunoglobulin. Currently few women in the UK refuse RAADP, so there is little scope for an increase in uptake. We consider that it may be possible that women who would refuse RAADP would also refuse high-throughput NIPT, but this should not impact on the cost-effectiveness of NIPT, only on throughput. While the clinical effectiveness review identified studies that reported the rate of uptake of anti-D

immunoglobulin among women provided with high-throughput NIPT, none provided a comparison with what uptake would have been in those same women without provision of high-throughput NIPT. We therefore assumed that women informed that they are carrying a RhD-positive fetus would be no more or less likely to uptake anti-D immunoglobulin than they would if offered RAADP. Some women who are told they are carrying a RhD-negative fetus may still demand RAADP, and this cost is not incorporated in the model. We conduct a two-way sensitivity analysis in which the uptake of RAADP is decreased or increased alongside the reduction of the uptake of post-partum anti-D immunoglobulin;

SA5. The base case analysis incorporates the rate of inconclusive high-throughput NIPT results found in the UK (Bristol) studies. The rate of inconclusive results will vary according to the local population demography because they are more likely in certain ethnic groups such as those of African ethnic origin. The rate of inconclusive results may also vary if the operation of the NIPT is different in a trial setting compared to in routine use, for example if less time is spent on reprocessing initially inconclusive test results. Increasing the rate of inconclusive test results where these are treated as test positive will increase the rate of false positive results and reduce the specificity of NIPT. This will in turn reduce the amount of unnecessary anti-D immunoglobulin and associated management costs that can be avoided through use of high-throughput NIPT;

SA6. We conduct a two-way sensitivity analysis in which the cost per dose of anti-D immunoglobulin therapy is varied alongside the cost per high-throughput NIPT. The cost of high-throughput NIPT to the NHS is uncertain for a number of reasons: (a) the unit cost varies by throughput and so will depend on the total uptake of the NIPT; (b) the unit cost of the test must be considered alongside other potential additional costs relating to transport of blood samples for testing, whether additional antenatal visits are required to draw blood and deliver test counselling and results; and (c) the royalty fee charged to the NHS in addition to the unit cost of the test is uncertain. The base case analysis includes a test cost of [redacted] and a royalty fee of [redacted] ([redacted]). The base case assumes that high-throughput NIPT can be incorporated in to routine antenatal care without imposing further marginal costs to the NHS, which is likely to be favourable to any 'test and RAADP' strategies. We calculate the threshold NHS cost per high-throughput NIPT at which the ICER for any strategy incorporating the NIPT falls below £20,000 and £30,000 per QALY. We also show how the ICER varies as the cost per test is varied between £13.20 and £24.20. The cost of anti-D immunoglobulin may be subject to discounts from the list prices utilised in the base case analysis. We show how the cost-effectiveness results vary to -20%, -10%, +10% and +20% of list price. The cost-effectiveness of any high-throughput NIPT will be reduced as the price

of anti-D immunoglobulin falls because the savings from avoiding unnecessary RAADP will be lower;

SA7. Since the introduction of RAADP there has been a move from the two-dose to the single-dose regimens for a variety of reasons as indicated in the recent anti-D immunoglobulin prophylaxis audit. We conducted a sensitivity analysis that assumes a 100% use of the cheaper of the two regimens, i.e. the single-dose.

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6.4.3 Model validation

PS developed the model and SG checked the model for errors. Comparisons across strategies were done to identify inconsistencies. Comparisons with the previous NICE TA 156 were also done to identify the sources of any potential discrepancy.

6.5 Results of the independent economic assessment

This section reports the results of the de-novo economic model developed to assess the cost-effectiveness of high-throughput NIPT to identify fetal RhD status in women who are RhD-negative and not known to be sensitised to the RhD antigen. The base case results for the different post-partum strategies are shown first, followed by the results of performing sensitivity analysis on key model input parameters. All results are based on the probabilistic analysis. Detailed characteristics of each post-partum scenario are provided in **Error! Reference source not found.**.

6.5.1 Base case results

Error! Reference source not found. presents the results for each post-partum testing scenario separately against current practice of 'No test and RAADP'. Total costs, total QALYs, incremental costs and incremental QALYs are presented together with incremental cost per QALY gained (ICER) and population net health benefits at £20,000 and £30,000 threshold values. The results of the model suggest that for each additional sensitisation there is a loss of approximately 0.9 QALYs. Any difference in QALYs between strategies is attributable wholly to the difference in the number of sensitisations.

Post-partum scenario 1 (NIPT PP1) describes the use of NIPT to guide RAADP only, with all women continuing to receive cord serology with FMH and post-partum anti-D immunoglobulin as required, irrespective of NIPT test result. This is estimated to reduce costs by £584,000 per 100,000 pregnancies and to result in lower health benefits (0.5 QALYs) than current practice.

Post-partum scenario 2 (NIPT PP2) describes the use of NIPT to guide both RAADP and post-partum care to women who test positive or in whom the results are inconclusive, where cord serology is provided only in these women to guide FMH and post-partum anti-D immunoglobulin as required. This is estimated to reduce costs compared to current practice by approximately £671,000 but to result in a loss of 19.1 QALYs per 100,000 pregnancies.

Post-partum scenario 3 (NIPT PP3) describes the use of NIPT to guide RAADP and post-partum anti-D immunoglobulin to women who test positive or inconclusive, and where cord serology is used to guide FMH and post-partum anti-D immunoglobulin as required only to women in whom the NIPT indicates a RhD-negative fetus. This is estimated to reduce costs compared to current practice by £485,000 but to result in a loss of 0.5 QALYs per 100,000 pregnancies.

Post-partum scenario 4 (NIPT PP4) describes the use of NIPT to guide both RAADP and post-partum FMH and anti-D immunoglobulin to women who test positive or inconclusive, and where cord serology is not provided. This is estimated to reduce costs compared to current practice by approximately £573,000 but results in a loss of 19.1 QALYs per 100,000 pregnancies.

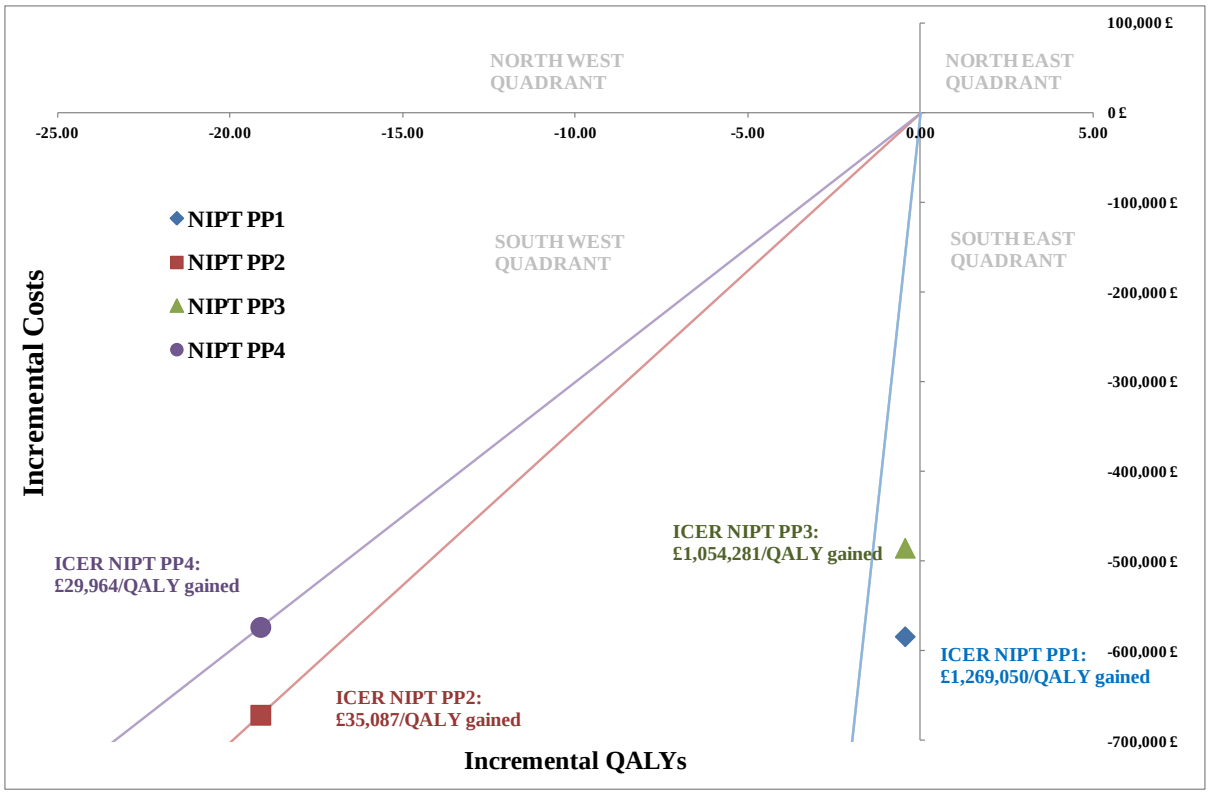
All post-partum scenarios are cost saving but also less effective than No test and RAADP, placing them on the south-west quadrant of the cost-effectiveness plane – see Figure 1. The least effective strategies are those that omit cord serology for women who test negative on the NIPT. Without cord serology false negatives are not picked up at delivery and are not provided with post-partum anti-D immunoglobulin. In the model, the additional health gains are determined by the management of high-throughput NIPT false negative test results.

Table 3 Incremental cost-effectiveness outcomes associated with high-throughput NIPT *vs* other strategies (base case post-partum scenarios) – probabilistic results

Strategies	Total costs	Total QALYs	Increm. Costs	Increm. QALYs	ICER (£/ QALY gained)	Population NHB (λ=£20,000)	Population NHB (λ=£30,000)
Current clinical practice							
No Test and RAADP	£15,983,725	2,433,756	---	---	---	2,432,957	2,433,223
Post-partum scenario 1 (NIPT PP1)							
Test and RAADP (T+ only) vs No Test and RAADP	£15,400,187	2,433,756	-£583,538	-0.46	£1,269,050	2,432,986	2,433,242
Post-partum scenario 2 (NIPT PP2)							
Test and RAADP (T+ only) vs No Test and RAADP	£15,312,630	2,433,737	-£671,095	-19.13	£35,087	2,432,972	2,433,227
Post-partum scenario 3 (NIPT PP3)							
Test and RAADP (T+ only) vs No Test and RAADP	£15,498,942	2,433,756	-£484,783	-0.46	£1,054,281	2,432,981	2,433,239
Post-partum scenario 4 (NIPT PP4)							
Test and RAADP (T+ only) vs No Test and RAADP	£15,410,610	2,433,737	-£573,114	-19.13	£29,964	2,432,967	2,433,223

Due to these NIPT strategies being less costly and less effective than No test and RAADP, the ICERs calculated in **Error! Reference source not found.** (and Figure 1) show the cost per QALY gained with current practice compared to high-throughput NIPT. Hence where the ICER is above the cost-effectiveness threshold this would support the use of NIPT (No test and RAADP vs NIPT PP1, ICER approximately £1,270,000 per QALY gained). The cost-effectiveness threshold can be used to present results in terms of net health benefits (NHB), in which case the comparison is more straightforward as the strategy with the highest NHB is preferred. All NIPT strategies have an expected NHB higher than No test and RAADP, both at threshold values of £20,000 and £30,000. Compared to No test and RAADP, NIPT PP1 has greater NHB (incremental NHB at £20,000 of approximately 14; incremental NHB at £30,000 of approximately 16, vs No test and RAADP).

Figure 1: Cost-effectiveness plane of current practice (No Test and RAADP) and alternative NIPT scenarios (PP1 to PP4).



The base case analysis assumes no adverse health impacts from use of a blood based product such as anti-D immunoglobulin. This is in line with the fact that widespread global use of anti-D immunoglobulin has yet to produce evidence for any adverse consequences. We illustrate how sensitive the ICER is to changes in these assumptions. Using the net benefit framework it is possible to interpret the results of the sensitivity analysis around price of anti-D immunoglobulin in terms of health impact. An increase of 20% in the cost of anti-D immunoglobulin represents a cost of £39.50*0.2 = £7.90. At a cost-effectiveness threshold of £20,000 per QALY this is equivalent to assuming a health cost of 7.9/20,000 = 0.0004 QALYs per administration, or a loss of 3.5 hours of full lifetime health from every woman per dose of anti-D immunoglobulin they receive.

The incremental costs of introducing NIPT can be broken down into the cost of the NIPT test, the cost of managing potentially sensitising events, the cost of RAADP, the cost of post-partum tests and anti-D immunoglobulin and the cost consequences of sensitisations, and this is shown in it is accumulated over multiple pregnancies and so is affected by the performance of strategy in terms of the number of sensitisations. Strategies with more sensitisations (NIPT PP2 and NIPT PP4) have marginally less test cost as sensitised women do not receive NIPT to guide RAADP in subsequent pregnancies (however, it is worth noting that the NIPT is recommended to be used in women who are sensitised in order to guide antenatal care).

Similarly all strategies save similar levels of costs from avoiding RAADP (approximately £1,544,000 per 100,000 pregnancies) and management of potentially sensitising events (approximately £626,000 per 100,000 pregnancies). The NIPT strategies vary more markedly in their impact on post-partum testing and anti-D immunoglobulin costs. Here NIPT PP1 is essentially the same as current practice, except for the small reduction in costs due to increased sensitisations, which makes women ineligible for FMH and anti-D immunoglobulin. NIPT PP2 decreases post-partum care costs by avoiding cord serology for women who test negative, but this comes at an increased cost of managing sensitisations as false negatives are not picked up at delivery nor provided with post-partum fetal maternal haemorrhage tests and anti-D immunoglobulin. NIPT PP3 increases post-partum care costs because while cord serology is avoided for those who test positive, this results in unnecessary use of fetal maternal haemorrhage tests and anti-D immunoglobulin amongst women who test false positive (which includes those who test inconclusive but carry a RhD negative baby). NIPT PP4 decreases post-partum care costs relative to current practice by avoiding cord serology for all women, and is a combination of NIPT PP2 and NIPT PP3. As might be expected, the added cost of managing sensitisations and their associated health consequences is largest for the strategies with more sensitisations (NIPT PP2 and NIPT PP4), and is very small for strategies NIPT PP1 and NIPT PP3 (approximately £1,700 per 100,000 pregnancies).

Table 4. While the added NIPT cost is similar across strategies at approximately £1,585,000 per 100,000 pregnancies,

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it is accumulated over multiple pregnancies and so is affected by the performance of strategy in terms of the number of sensitisations. Strategies with more sensitisations (NIPT PP2 and NIPT PP4) have marginally less test cost as sensitised women do not receive NIPT to guide RAADP in subsequent pregnancies (however, it is worth noting that the NIPT is recommended to be used in women who are sensitised in order to guide antenatal care). Similarly all strategies save similar levels of costs from avoiding RAADP (approximately £1,544,000 per 100,000 pregnancies) and management of potentially sensitising events (approximately £626,000 per 100,000 pregnancies). The NIPT strategies vary more markedly in their impact on post-partum testing and anti-D immunoglobulin costs. Here NIPT PP1 is essentially the same as current practice, except for the small reduction in costs due to increased sensitisations, which makes women ineligible for FMH and anti-D immunoglobulin. NIPT PP2 decreases post-partum care costs by avoiding cord serology for women who test negative, but this comes at an increased cost of managing sensitisations as false negatives are not picked up at delivery nor provided with post-partum fetal maternal haemorrhage tests and anti-D immunoglobulin. NIPT PP3 increases post-partum care costs because while cord serology is avoided for those who test positive, this results in unnecessary use of fetal maternal haemorrhage tests and anti-D immunoglobulin amongst women who test false positive (which includes those who test inconclusive but carry a RhD negative baby). NIPT PP4 decreases post-partum care costs relative to current practice by avoiding cord serology for all women, and is a combination of NIPT PP2 and NIPT PP3. As might be expected, the added cost of managing sensitisations and their associated health consequences is largest for the strategies with more sensitisations (NIPT PP2 and NIPT PP4), and is very small for strategies NIPT PP1 and NIPT PP3 (approximately £1,700 per 100,000 pregnancies).

Table 4 Breakdown of incremental costs of high-throughput NIPT strategies *vs* No test and RAADP

Cost item	NIPT PP1	NIPT PP2	NIPT PP3	NIPT PP4
NIPT testing 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
Post-partum 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

The assumption that the results of the NIPT can be used to avoid all costs associated with the management of potentially sensitising events is favourable to NIPT, and £626,000 represents the maximum cost saving in this regard. If this cost saving is reduced to £52,000, i.e. if 92% of potentially sensitising events occur prior to the results of the NIPT being known, the ICER for No test and RAADP compared to NIPT PP1 would fall below £20,000 per QALY. The results of the audit indicate that 80% of potentially sensitising events occur after 20 weeks' gestation. This suggests that incorporating NIPT into routine antenatal care where it would be provided in week 20 or earlier (see **Error! Reference source not found.** for schedule of appointments) could avoid upward of 80% of the cost of managing potentially sensitising events.

We calculated the probability that each strategy would be cost-effective compared to No test and RAADP for each pair-wise comparison. NIPT PP1 and NIPT PP3 both have 99% probability of being cost-effective at threshold of £20,000 per QALY. NIPT PP2 and NIPT PP4 have a lower probability of being cost-effective at £20,000 per QALY, no higher than 73% when compared to No test and RAADP.

approximately 19 additional QALYs per 100,000 pregnancies, at approximately £88,000 additional cost, corresponding to an ICER of around £5,000 per QALY gained.

In NIPT PP3 cord serology is used to identify false negative results, but withheld in women with inconclusive results or for whom the NIPT indicates a RhD-positive fetus (in favour of FMH and anti-D immunoglobulin). Compared to NIPT PP1, the QALY gain is not affected as the model assumes no adverse health benefits from unnecessary use of anti-D immunoglobulin. As NIPT PP3 is more costly than NIPT PP1, in the base case it is dominated by NIPT PP1.

No Test and RAADP is more costly than NIPT PP1, and is the most effective strategy. The administration of RAADP and supplementary anti-D immunoglobulin for potentially sensitising events among the false negatives leads to an additional 0.5 QALYs per 100,000 pregnancies compared to NIPT PP1, at an additional cost of £584,000. This means that the ICER for No Test and RAADP compared to NIPT PP1 is £1,270,000. Using high-throughput NIPT and performing cord serology irrespective of the result (NIPT PP1) has higher NHB compared to any other strategy.

Table 5 presents the fully incremental cost-effectiveness probabilistic results for high-throughput NIPT vs other strategies. Fully incremental results do not compare each NIPT

strategy to current practice (i.e. No test and RAADP) but compare all NIPT scenarios simultaneously as competing alternative strategies. In this table strategies are ranked by total costs and total QALYs, with the cheapest strategy coming first (NIPT PP2). Dominated strategies (those that have higher costs than more effective strategies) are at the bottom rows of the table. Incremental costs, incremental QALYs and consequently the incremental cost effectiveness ratio (ICER) are incremental to the strategy in the row above. The same applies to the incremental net health benefits (INHB) at £20,000 and £30,000 threshold values.

In NIPT PP2 cord serology is used to identify false positive results, thereby avoiding unnecessary FMH and anti-D immunoglobulin in these women, but is withheld in women for whom the NIPT indicates a RhD-negative fetus. Using the negative results of high-throughput NIPT to rule out post-partum cord serology, FMH and anti-D immunoglobulin (NIPT PP2 and NIPT PP4) has lower QALYs compared to No test and RAADP, NIPT PP1 and NIPT PP3. While there are further cost savings from avoiding post-partum cord serology and anti-D immunoglobulin, the majority of sensitisations occur and can be prevented by the administration of anti-D immunoglobulin at delivery. NIPT PP2 is the cheapest strategy, and provides the same QALYs as NIPT PP4. Hence NIPT PP4 is dominated by NIPT PP2.

Providing CS to all women, as with NIPT PP1, will identify both the false positive (the small number of false positives and the proportion of women with inconclusive results who are carrying RhD-negative babies) and false negative results. While NIPT PP1 has higher costs compared to NIPT PP2 due to the additional cord serology tests, these are offset somewhat by cost savings from avoiding sensitisations in false negatives. Compared to NIPT PP2, NIPT PP1 is estimated to provide

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approximately 19 additional QALYs per 100,000 pregnancies, at approximately £88,000 additional cost, corresponding to an ICER of around £5,000 per QALY gained.

In NIPT PP3 cord serology is used to identify false negative results, but withheld in women with inconclusive results or for whom the NIPT indicates a RhD-positive fetus (in favour of FMH and anti-D immunoglobulin). Compared to NIPT PP1, the QALY gain is not affected as the model assumes no adverse health benefits from unnecessary use of anti-D immunoglobulin. As NIPT PP3 is more costly than NIPT PP1, in the base case it is dominated by NIPT PP1.

No Test and RAADP is more costly than NIPT PP1, and is the most effective strategy. The administration of RAADP and supplementary anti-D immunoglobulin for potentially sensitising events among the false negatives leads to an additional 0.5 QALYs per 100,000 pregnancies compared to NIPT PP1, at an additional cost of £584,000. This means that the ICER for No Test and RAADP compared to NIPT PP1 is £1,270,000. Using high-throughput NIPT and performing cord serology irrespective of the result (NIPT PP1) has higher NHB compared to any other strategy.

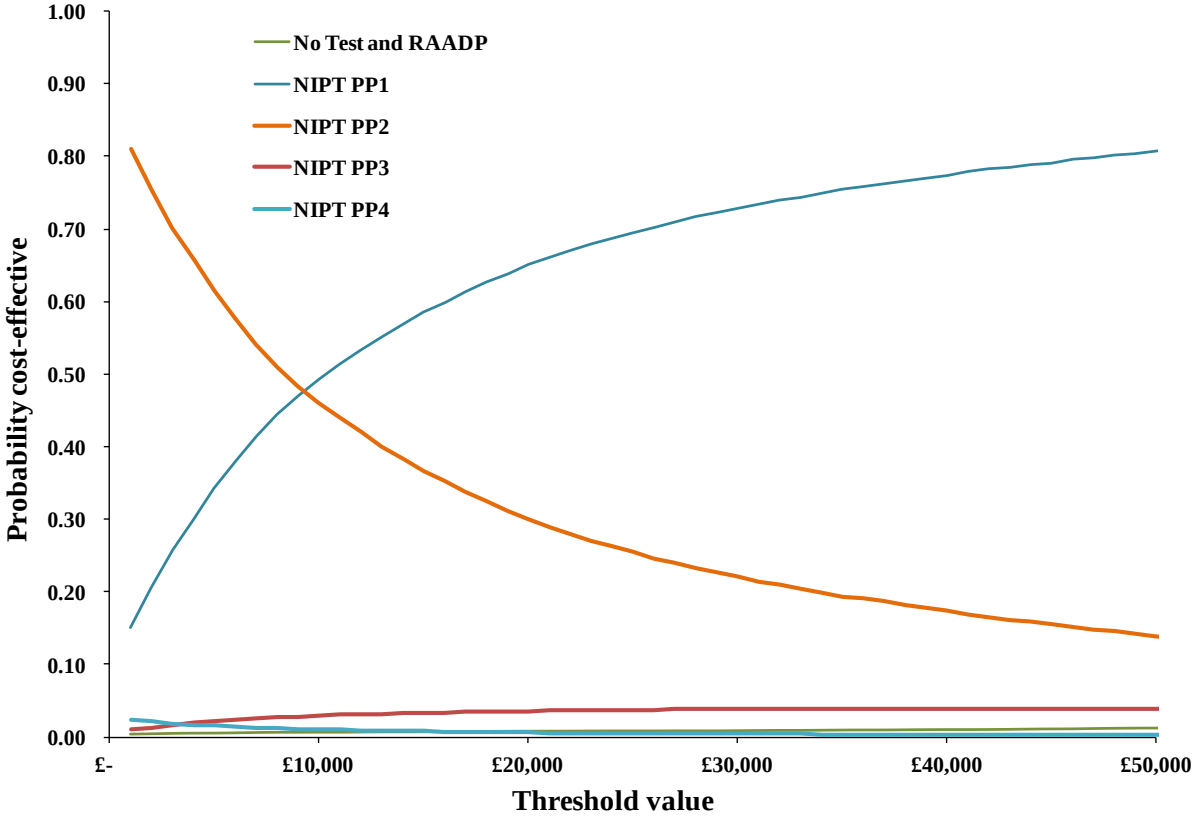
Table 5 Fully incremental cost-effectiveness outcomes associated with high-throughput NIPT *vs* other strategies (base case post-partum scenarios) – probabilistic results

Strategies	Total costs	Total QALYs	Incr. Costs	Incr. QALYs	ICER (£/QALY gained)	Population INHB (λ=£20,000)	Population INHB (λ=£30,000)
NIPT PP2	£15,312,630	2,433,737	---	---	---	---	---
NIPT PP1	£15,400,187	2,433,756	£87,557	18.67	£4,690	14	16
No Test and RAADP	£15,983,725	2,433,756	£583,538	0.46	£1,269,050	-29	-19
NIPT PP4	£15,410,610	2,433,737	---	---	Dominated	---	---
NIPT PP3	£15,498,942	2,433,756	---	---	Dominated	---	---

The decision uncertainty can be shown graphically with a cost-effectiveness acceptability curve (CEAC). Figure 2 shows the CEACs for the different scenarios being compared (i.e. No test and RAADP and alternative high-throughput NIPT scenarios - PP1 to PP4) in which we can depict the probability that each strategy is cost-effective for a range of threshold values. When all strategies are simultaneously compared, for threshold values of £20,000 and

£30,000, the highest probability of being cost-effective is obtained by NIPT PP1 with 0.65 and 0.73, respectively. For the same threshold values, the probability of NIPT PP2 being cost-effective is 0.30 and 0.22, respectively. NIPT PP1 is the alternative with the highest probability of being cost-effective and also expected cost-effective alternative for thresholds above £10,000. An estimate of the maximum value of further research, the EVPI, is estimated to be approximately £203,000 considering 10 years of cohorts of 100,000 pregnancies and using a cost-effectiveness threshold of £20,000 per QALY. If research to reduce uncertainty in the model values would cost more than £203,000 this suggests that it would not represent a good investment.

Figure 2: Cost-effectiveness acceptability curves of current practice (No Test and RAADP) and alternative NIPT scenarios (PP1 to PP4).



6.5.2 Sensitivity analyses results

Several sensitivity analyses were carried out to assess the sensitivity of the base-case cost per QALY findings, as detailed in **Error! Reference source not found.**. We assessed the impact of using pooled evidence from all relevant NIPT accuracy evidence rather than UK Bristol studies only and, by using recent evidence from a UK study [1], assessed the performance of high-throughput NIPT at different gestation periods. An analysis over the NIPT inconclusive results was also performed by replacing the pooled estimates for the sensitivity and specificity with the individual study results. Sensitivity analysis was performed on the effectiveness of

RAADP by using a different sensitisation rate pooled from a larger number of studies. An assessment was also done over the uptake rates for RAADP and post-partum anti-D immunoglobulin, with and without NIPT, decreasing these to the circumstances when the correct dose at the correct time was administered according to recent evidence [21]. Additionally, we analysed the impact of altering the cost of the diagnostic test and the cost of treatment, two key components of this

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assessment as highlighted in the relevant literature. Finally, we have evaluated the impact of reducing the cost of the fetal-maternal haemorrhage test and, under an alternative post-partum scenario, assessed the management of high-throughput inconclusive results separately to the positive test results. The following sections look closely at each of these analyses and provide interpretations of obtained results relatively to the base case findings.

6.5.2.1 SA1: Sensitivity analysis over the NIPT accuracy using all relevant evidence

Error! Not a valid bookmark self-reference. shows the results when diagnostic accuracy for high-throughput NIPT accuracy is based on all available studies as opposed to UK (Bristol) studies only. This increases the pooled specificity by 2%, while the pooled sensitivity levels are reduced by only 0.2% – see section 4.2.2. Compared to the base case, the 2% reduction in false positive results allows for more avoidance of anti-D immunoglobulin and associated tests, reducing total costs across all NIPT strategies by between £20,000 and £150,000 per 100,000 pregnancies. Total QALYs are marginally affected by the small 0.2% increase in false negatives, with NIPT PP2 and NIPT PP4 being the most affected as these assume no use of cord serology post-partum for women with negative results. Compared to the base case, this results in a further loss of approximately 12 QALYs per 100,000 pregnancies. Compared to No test and RAADP, NIPT PP2 and NIPT PP3 are still found to be cost saving (approximately £630,000 to £690,000 per 100,000 pregnancies), but NIPT PP3 is associated with a loss of approximately 1 QALY per 100,000 pregnancies compared with a loss of 31 with NIPT PP2. NIPT PP1 and NIPT PP3 are the only strategies to offer increased net health benefits compared to No Test and RAADP, with ICERs for No Test and RAADP of approximately £830,000.

Table 6 Incremental cost-effectiveness outcomes associated with high-throughput NIPT *vs* other strategies - all NIPT accuracy evidence – probabilistic results

Strategies	Total costs	Total QALYs	Increm. Costs	Increm. QALYs	ICER (£/ QALY gained)	Population NHB (λ=£20,000)	Population NHB (λ=£30,000)
Current clinical practice – all NIPT accuracy evidence pooled							
No Test and RAADP	£15,983,725	2,433,756	---	---	---	2,432,957	2,433,223
Post-partum scenario 1 (NIPT PP1) – all NIPT accuracy evidence pooled							
Test and RAADP (T+ only) vs No Test and RAADP	£15,353,678	2,433,756	-£630,047	-0.76	£829,196	2,432,988	2,433,244
Post-partum scenario 2 (NIPT PP2) – all NIPT accuracy evidence pooled							
Test and RAADP (T+ only) vs No Test and RAADP	£15,291,035	2,433,725	-£692,690	-31.13	£22,253	2,432,961	2,433,215
Post-partum scenario 3 (NIPT PP3) - all NIPT accuracy evidence pooled							
Test and RAADP (T+ only) vs No Test and RAADP	£15,351,238	2,433,756	-£632,487	-0.76	£832,406	2,432,988	2,433,244
Post-partum scenario 4 (NIPT PP4) - all NIPT accuracy evidence pooled							
Test and RAADP (T+ only) vs No Test and RAADP	£15,286,779	2,433,725	-£696,946	-31.13	£22,390	2,432,961	2,433,216

6.5.2.2 SA2: Sensitivity analysis over the NIPT accuracy at different timings using Chitty et al

Table 7 presents the results of providing the high-throughput NIPT test at different gestation periods. These are based on the analysis by Chitty et al (see Section 4.2.2), with the sensitivity and specificity repeated in for information. In this analysis, only the diagnostic accuracy is varied from the base case values of 0.998 for sensitivity and 0.942 for specificity, which impacts on the probability of sensitisation. The sensitivity estimate is least favourable at 14-17 weeks' gestation and the specificity estimate is least favourable at 18-23 weeks' gestation, although these differences may be due to random chance rather than systematic variation between these time points. While this analysis does not directly take into consideration the impact of the test timing on the potential to avoid costs associated with the management of a potentially sensitising events, we estimate the threshold amount of these costs that would have to occur prior to the NIPT in order for the ICER to cross the threshold of £20,000 per QALY gained. Thus, results are only shown for the best NIPT strategy within each period.

As for the base case, the introduction of high-throughput NIPT results in lower health benefits when compared to No test and RAADP. This happens irrespectively of the timing at which

the test is carried out. The QALY loss is slightly greater when performing NIPT at 14-17 weeks' gestation due to the very small drop in sensitivity of 0.002, leading to more false negatives and a loss of

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approximately 1 QALY per 100,000 pregnancies compared to current practice, rather than a loss of approximately 0.4 QALYs if NIPT is provided between 11-13 weeks or 18-23 weeks. The cost saving is greatest at 14-17 weeks' due to the increase in specificity as fewer false positive results result in less unnecessary treatment.

Table 7 Incremental cost-effectiveness outcomes associated with high-throughput NIPT at different timings vs other strategies (post-partum scenarios) – based on Chitty et al – probabilistic results

Strategies	Sensitivity	Specificity	Total costs	Total QALYs	Increm. Costs	Increm. QALYs	ICER (£/ QALY gained)	Pop. NHB (λ=£20,000)	Pop. NHB (λ=£30,000)
Current clinical practice – irrespective of NIPT test timing (Chitty et al [1])									
No Test and RAADP	---	---	£15,983,725	2,433,756	---	---	---	2,432,957	2,433,223
Best post-partum scenario when NIPT testing performed at 11-13 weeks' gestation (Chitty et al [1])									
NIPT PP1 (vs No Test and RAADP)	0.9983	0.9525	£15,378,009	2,433,756	-£605,716	-0.39	£1,536,731	2,432,987	2,433,243
Best post-partum scenario when NIPT testing performed at 14-17 weeks' gestation (Chitty et al [1])									
NIPT PP1 (vs No Test and RAADP)	0.9967	0.9534	£15,370,718	2,433,756	-£613,007	-0.77	£797,046	2,432,987	2,433,243
Best post-partum scenario when NIPT testing performed at 18-23 weeks' gestation (Chitty et al [1])									
NIPT PP1 (vs No Test and RAADP)	0.9982	0.9304	£15,429,067	2,433,756	-£554,658	-0.36	£1,529,418	2,432,984	2,433,242

The base case results suggest that NIPT PP1 provides savings of £626,000 from avoiding the costs of managing potentially sensitising events. The audit [21] indicates that 80% of potentially sensitising events occur after week 20. If NIPT PP1 is provided between 18-23 weeks' gestation and £547,000 or 87% of the cost of managing potentially sensitising events occurs prior to the test, the ICER for No test and RAADP would fall below £20,000 per QALY gained. If NIPT PP3 is provided between 11-13 weeks' or 14-17 weeks' gestation, then approximately £598,000 or 95% of the cost of managing potentially sensitising events would have to occur prior to the test in order for the ICER for No test and RAADP to fall below £20,000 per QALY gained.

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6.5.2.3 SA3: Sensitivity analysis on the effectiveness of RAADP using Turner et al

Findings from Turner et al [79] estimated a pooled odds ratio estimate for sensitisation under RAADP (*vs* No RAADP, only post-partum anti-D immunoglobulin) of 0.31 rather than 0.37 as in the NICE TA 156 [72] (**Error! Not a valid bookmark self-reference.**) **Error! Not a valid bookmark self-reference.**. Compared to base case results (**Error! Reference source not found.**) the marginal reduction on the sensitisation rate (less 0.05%) brings minimal changes to the total costs and QALYs estimates, as expected. The increase in effectiveness of RAADP provides reductions in total costs for all strategies and minor changes in the QALY loss associated with NIPT.

Table 8 Incremental cost-effectiveness outcomes associated with high throughput NIPT vs other strategies (post-partum scenarios) – based on Turner et al [79] pooled RAADP effectiveness – probabilistic results

Strategies	Total costs	Total QALYs	Increm. Costs	Increm. QALYs	ICER (£/ QALY gained)	Population NHB (λ=£20,000)	Population NHB (λ=£30,000)
Current clinical practice – Turner et al [79] pooled RAADP effectiveness							
No Test and RAADP	£15,923,756	2,433,774	---	---	---	2,432,978	2,433,243
Post-partum scenario 1 (NIPT PP1) – Turner et al [79] pooled RAADP effectiveness							
Test and RAADP (T+ only) vs No Test and RAADP	£15,339,945	2,433,773	-£583,811	-0.50	£1,164,285	2,433,006	2,433,262
Post-partum scenario 2 (NIPT PP2) – Turner et al [79] pooled RAADP effectiveness							
Test and RAADP (T+ only) vs No Test and RAADP	£15,252,388	2,433,755	-£671,369	-19.17	£35,018	2,432,992	2,433,246
Post-partum scenario 3 (NIPT PP3) – Turner et al [79] pooled RAADP effectiveness							
Test and RAADP (T+ only) vs No Test and RAADP	£15,438,716	2,433,773	-£485,040	-0.50	£967,307	2,433,001	2,433,259
Post-partum scenario 4 (NIPT PP4) – Turner et al [79] pooled RAADP effectiveness							
Test and RAADP (T+ only) vs No Test and RAADP	£15,350,384	2,433,755	-£573,372	-19.17	£29,906	2,432,987	2,433,243

6.5.2.4 SA4: Sensitivity analysis on the uptake of RAADP and post-partum anti-D immunoglobulin

In the base case analysis our estimates of compliance are based on the use of anti-D immunoglobulin in women who are eligible in terms of RhD status, ignorance of the father's status and remain pregnant to receive RAADP. The National Comparative Audit of Blood

Transfusion 2013 on Anti-D Immunoglobulin Prophylaxis [21] reported that, out of all RhD-negative women, 87.5% received the correct dose at the correct time of RAADP. Furthermore, it reported that 91.6% received the correct dose at the correct time of post-partum anti-D immunoglobulin prophylaxis. We made use of these estimates to provide a lower bound for compliance with anti-D immunoglobulin. As for the base case, it was assumed that the use of high-throughput NIPT does not influence the uptake with anti-D

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immunoglobulin, that is the uptake rate is the same irrespective if NIPT was previously accepted/administered.

Error! Not a valid bookmark self-reference. presents the incremental cost-effectiveness outcomes for each alternative scenario when different RAADP and post-partum anti-D immunoglobulin uptake rates are used. As the sensitivity analysis does not impact on the rank order of the alternative post-partum scenarios, the results are shown for NIPT PP1 only i.e. out of the five alternatives being compared, the results for the best strategy is shown together with current practice. Base case results correspond to 99.0% and 98.4% uptake with RAADP and post-partum anti-D immunoglobulin, respectively. Overall the results are robust to reduced compliance and there is little impact on incremental comparison between NIPT PP1 and No test and RAADP. The cost for all strategies is increased if compliance with a cost-effective treatment such as RAADP is reduced, while the QALY loss associated with additional sensitisations is slightly reduced.

Table 9 Incremental cost-effectiveness outcomes associated with high throughput NIPT vs other strategies (post-partum scenarios) – different uptake rates of RAADP and post-partum anti-D immunoglobulin – probabilistic results of the two best strategies for each analysis are shown

Strategies	Total costs	Total QALYs	Increm. Costs	Increm. QALYs	ICER (£/ QALY gained)	Population NHB (λ=£20,000)	Population NHB (λ=£30,000)
Base case anti-D immunoglobulin uptake rates – RAADP at 99.0% and post-partum at 98.4%							
No Test and RAADP	£15,983,725	2,433,756	---	---	---	2,432,957	2,433,223
NIPT PP1 (vs No Test and RAADP)	£15,400,187	2,433,756	-£583,538	-0.46	£1,269,050	2,432,986	2,433,242
Anti-D immunoglobulin uptake rates – RAADP at 87.5% and post-partum at 98.4%							
No Test and RAADP	£16,060,984	2,433,733	---	---	---	2,432,930	2,433,198
NIPT PP1 (vs No Test and RAADP)	£15,477,810	2,433,733	-£583,174	-0.41	£1,430,198	2,432,959	2,433,217
Anti-D immunoglobulin uptake rates – RAADP at 99.0% and post-partum at 91.6%							
No Test and RAADP	£16,029,705	2,433,743	---	---	---	2,432,941	2,433,208
NIPT PP1 (vs No Test and RAADP)	£15,446,384	2,433,742	-£583,321	-0.43	£1,360,214	2,432,970	2,433,227
Anti-D immunoglobulin uptake rates – RAADP at 87.5% and post-partum at 91.6%							
No Test and RAADP	£16,101,601	2,433,721	---	---	---	2,432,916	2,433,185
NIPT PP1 (vs No Test and RAADP)	£15,518,619	2,433,721	-£582,982	-0.38	£1,532,578	2,432,945	2,433,204

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Figure 3: Specificity by rate of high-throughput NIPT inconclusive results per study.

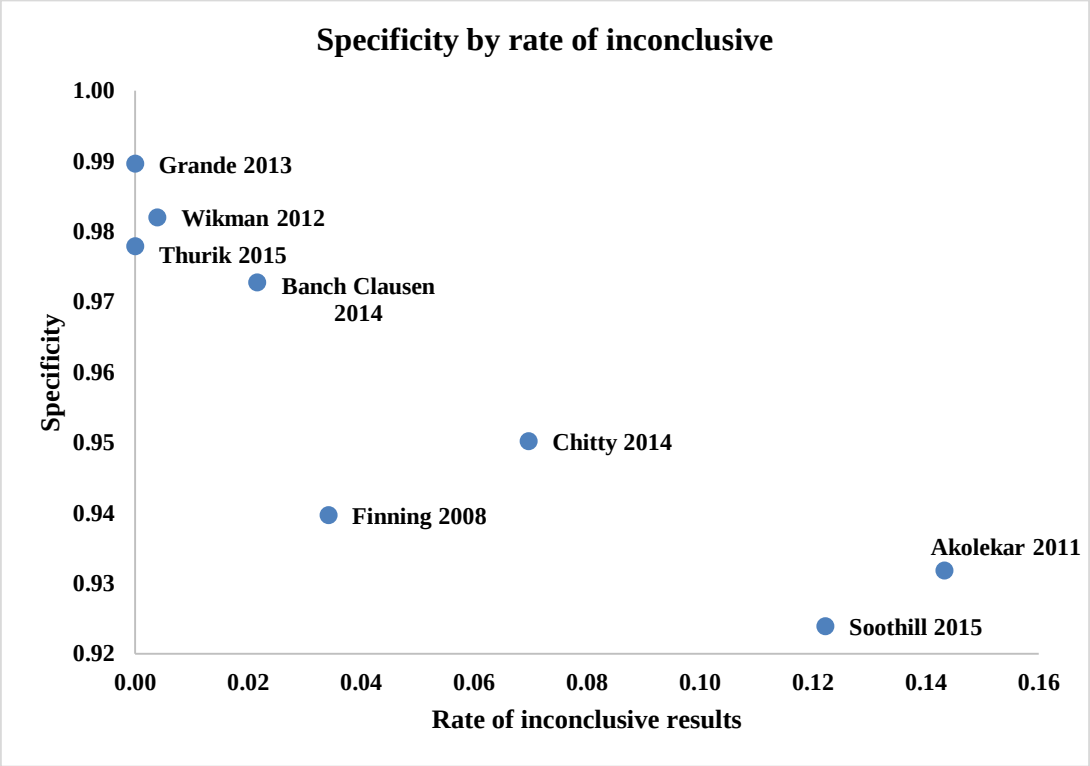


Figure 16: Population net health benefits for all NIPT strategies by rate of NIPT inconclusive results per study.

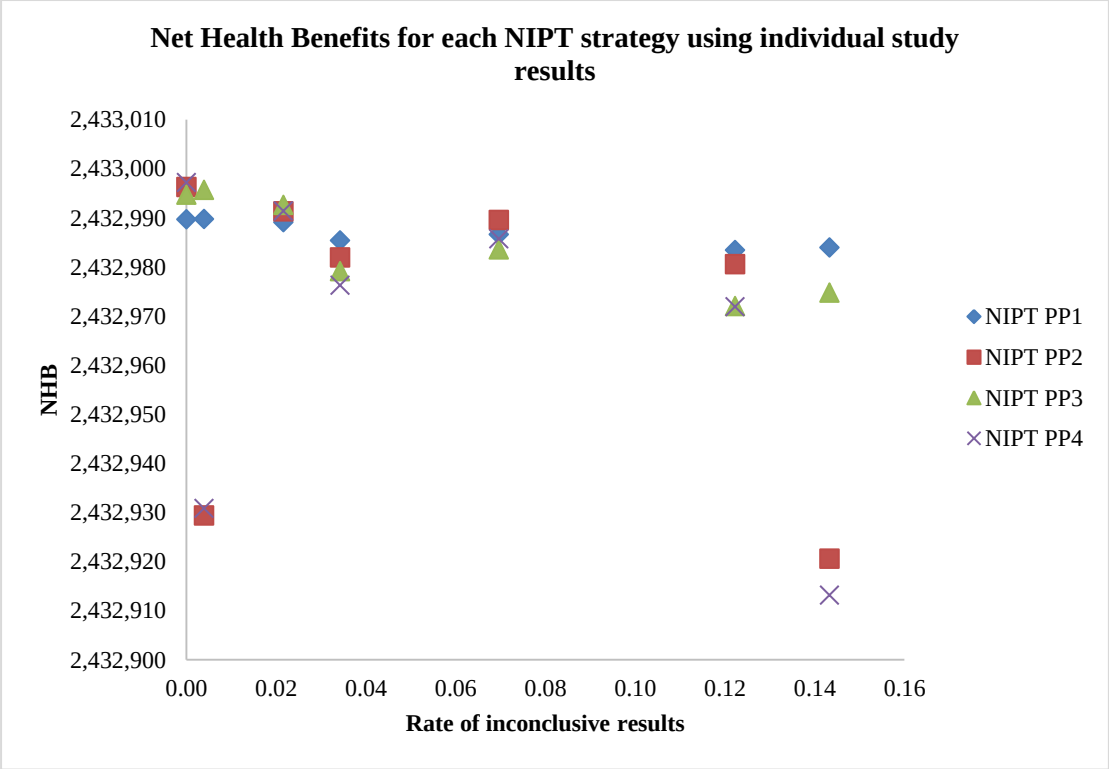
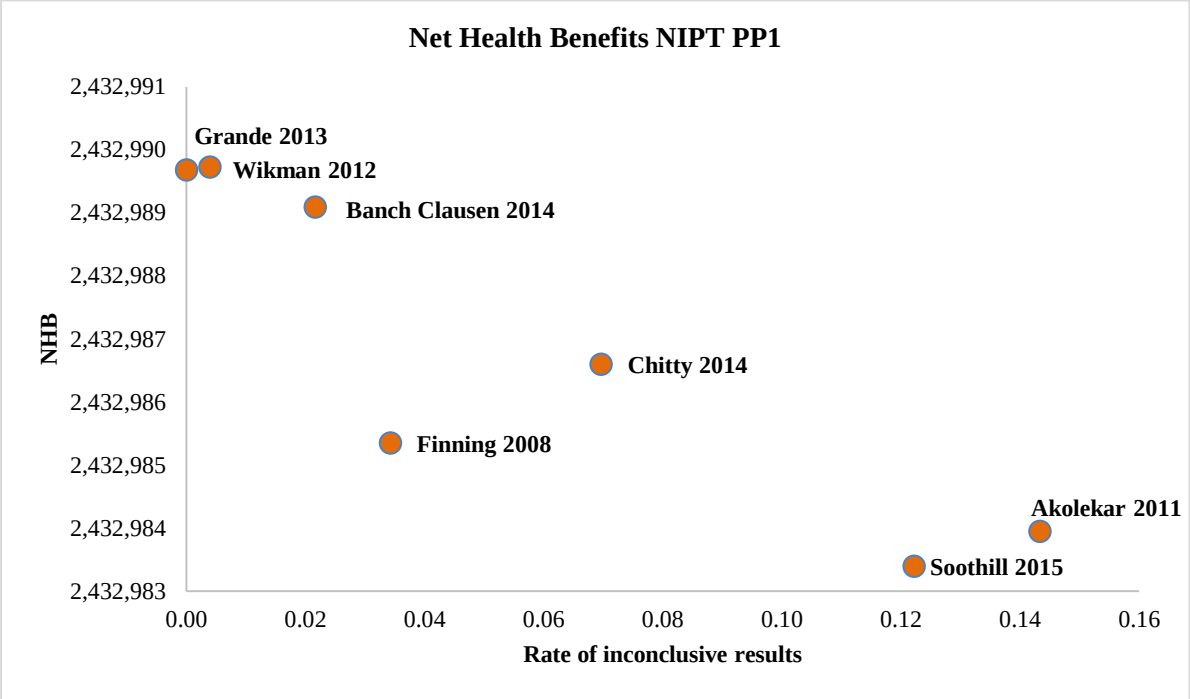


Figure 4: Population net health benefits for NIPT PP1 by rate of NIPT inconclusive results per study.



6.5.2.6 SA6: Sensitivity analysis on NIPT and Anti-D costs

The unit cost of an NIPT is subject to some uncertainty as it depends on throughput (the total number of samples per year) and the level of the royalty fee. The throughput determines how many machines must be bought and at what capacity they are utilised. The base case analysis assumed sufficient machines to process all pregnancies in England in a given year. Further to this, the introduction of the NIPT may impose additional costs in routine antenatal care in terms or appointments and staff time. Similarly, the cost of anti-D immunoglobulin may depart from the list price on the basis of negotiated discounts.

The results of a two-way analysis around these unit costs reported in **Error! Reference source not found.** show that the base case is very sensitive to both the price of NIPT and the price of anti-D-. The x-axis represents the range of anti-D immunoglobulin cost from -20% to +20%. This increase/decrease in the cost of anti-D immunoglobulin is applied to all occasions in which the treatment is administered and, thus, the RAADP cost shown is only indicative as the estimated cost of anti-D for potentially sensitising events and for post-partum, as described in Section 6.3.12, are omitted. The y-axis represents the range of costs per high-throughput NIPT test from £17.6 to £28.6 (which may for example be interpreted as a range between £16 and £26 with an additional [redacted] royalty fee). A small increase in price of high-throughput NIPT would result in NIPT PP1 no longer offering the highest population net health benefit. In fact, raising the cost per high-throughput NIPT test to [redacted] implies a

switch to No test and RAADP being the strategy offering highest net health benefits. Similar results were found when the cost-effectiveness threshold is £20,000 or £30,000. NIPT PP1 strategy is always preferred over other post-partum strategies (PP2, PP3 or PP4). At no point would the price of anti-D immunoglobulin be high enough to make the omission of post-partum anti-D immunoglobulin (NIPT PP2 and NIPT PP 4) look cost-effective.

Figure 18: Cost-effectiveness outcomes associated with NIPT high throughput vs other strategies (post-partum scenarios) across a range of NIPT* and Anti-D costs – probabilistic results for thresholds of £20,000/QALY gained and £30,000/QALY.**

* NIPT cost includes a royalty fee of [redacted] over the NIPT price;
** The decrease/increase of RAADP cost was applied to the different RAADP dosages used routinely at 28-32 wks, at potentially sensitising events or post-partum. For illustrative purposes, however, the decrease/increase shown is for an anti-D of 1500 UI (Rhophylac – BNF price);
*** Location of the base case with a cost of high-throughput NIPT of [redacted].

6.5.2.7 SA7: Sensitivity analysis over the Fetal-maternal haemorrhage test cost

Reducing the cost of fetal-maternal haemorrhage test to £3.17 (Szczepura et al [61], updated to 2015 prices) halves the estimated total costs of all strategies when compared to the total costs of the base case scenarios - see Table 10. Estimated total QALYs are similar to base case findings. NIPT PP1 is now less cost saving compared to current practice. This is explained by the use of fetal-maternal haemorrhage test in the management of potentially sensitising events. When the cost of fetal-maternal haemorrhage test is reduced, the savings from avoiding the management of potentially sensitising events are reduced. All NIPT strategies still reduce costs compared to No test and RAADP, but by a lesser amount. This causes the ICER No Test and RAADP compared to NIPT PP2 and NIPT PP4 to fall below £20,000 per QALY.

Table 10 Incremental cost-effectiveness outcomes associated with high-throughput NIPT *vs* other strategies (post-partum scenarios) – Fetal-maternal haemorrhage test cost reduced – probabilistic results

Strategies	Total costs	Total QALYs	Increm. Costs	Increm. QALYs	ICER (£/ QALY gained)	Population NHB (λ=£20,000)	Population NHB (λ=£30,000)
Current clinical practice							
No Test and RAADP	£8,132,447	2,433,756	---	---	---	2,433,350	2,433,485
Post-partum scenario 1 (NIPT PP1)							
Test and RAADP (T+ only) vs No Test and RAADP	£7,986,460	2,433,756	-£145,987	-0.46	£317,485	2,433,356	2,433,490
Post-partum scenario 2 (NIPT PP2)							
Test and RAADP (T+ only) vs No Test and RAADP	£7,915,559	2,433,737	-£216,888	-19.13	£11,339	2,433,341	2,433,473
Post-partum scenario 3 (NIPT PP3)							
Test and RAADP (T+ only) vs No Test and RAADP	£7,846,684	2,433,756	-£285,763	-0.46	£621,464	2,433,363	2,433,494
Post-partum scenario 4 (NIPT PP4)							
Test and RAADP (T+ only) vs No Test and RAADP	£7,775,584	2,433,737	-£356,862	-19.13	£18,658	2,433,348	2,433,478

6.5.2.8 SA8: Sensitivity analysis on post-partum management of inconclusive results

The post-partum scenarios specified in the decision problem applied cord serology, fetal-maternal haemorrhage testing and post-partum anti-D immunoglobulin according to whether the results of the NIPT were positive or negative. In this regard, we grouped inconclusive results with NIPT positive results. However, in terms of post-partum management it may be worthwhile to regard those with inconclusive results as distinct from those on whom the NIPT indicates an RhD positive fetus. This would allow cord serology to be provided to women with negative results in order to identify false negatives and cord serology to be provided to women with inconclusive results in order to identify false positives, but for cord serology to be withheld in women with in whom the NIPT indicates a RhD positive fetus. This would result in total costs of £15,230,372 and 2,433,756 QALYs per 100,000 pregnancies. This post-partum approach would dominate all other NIPT strategies, and the ICER for No test and RAADP versus this strategy would be £1,638,356 per QALY gained.

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Error! Reference source not found. summarises the results of the base case analysis and the key sensitivity analyses.

Table 34 Summary of base case and key sensitivity analysis results

Analysis	Total		*vs* No test and RAADP (current practice)	*vs* next best strategy	
	Cost	**QALYs**	**ICER**	**ICER**	**Comparator**
Base Case					
No test and RAADP	£15,983,725	2,433,756	---	£1,269,050	NIPT PP1
NIPT PP1	£15,400,187	2,433,756	£1,269,050	£4,690	NIPT PP2
NIPT PP2	£15,312,630	2,433,737	£35,087	---	---
NIPT PP3	£15,498,942	2,433,756	£1,054,281	---	---
NIPT PP4	£15,410,610	2,433,737	£29,964	---	---
SA1 - Bivariate meta-analysis of all studies					
No test and RAADP	£15,983,725	2,433,756	---	£834,396	NIPT PP3
NIPT PP1	£15,353,677	2,433,756	£831,178	---	---
NIPT PP2	£15,291,034	2,433,725	£22,255	---	---
NIPT PP3	£15,351,238	2,433,756	£834,396	£2,123	NIPT PP4
NIPT PP4	£15,286,779	2,433,725	£22,391	---	---
SA2 - High-throughput NIPT performance assessed at different gestation periods (Chitty et al 2014)					
11 – 13 weeks' gestation					
No test and RAADP	£15,983,725	2,433,756	---	£1,536,731	NIPT PP1
NIPT PP1	£15,378,0	2,765,228	£1,165,229	£3,190	NIPT PP4

Analysis	Total		*vs* No test and RAADP (current practice)	*vs* next best strategy	
	Cost	QALYs	ICER	ICER	Comparator
NIPT PP2	£15,283,208	2,765,206	£31,462	---	---
NIPT PP3	£15,420,079	2,765,228	£1,084,295	---	---
NIPT PP4	£15,325,344	2,765,206	£29,573	---	---
14 – 17 weeks' gestation					
No test and RAADP	£15,983,725	2,433,756	---	£797,046	NIPT PP1
NIPT PP1	£15,370,717	2,433,756	£604,062	£678	NIPT PP4
NIPT PP2	£15,310,563	2,433,724	£15,604	---	---
NIPT PP3	£15,409,227	2,433,756	£566,114	---	---
NIPT PP4	£15,349,062	2,433,724	£14,712	---	---
18 – 23 weeks' gestation					
No test and RAADP	£15,983,725	2,433,756	---	£1,529,418	NIPT PP1
NIPT PP1	£15,429,066	2,433,756	£1,162,227	£6,209	NIPT PP2
NIPT PP2	£15,334,643	2,433,741	£31,744	---	---
NIPT PP3	£15,593,754	2,433,756	£817,141	---	---
NIPT PP4	£15,499,308	2,433,741	£23,691	---	---
SA3 - Sensitisation rate from Turner et al 2012					
No test and RAADP	£15,923,756	2,433,774	---	£1,164,285	NIPT PP1
NIPT PP1	£15,339,9	2,433,773	£1,164,285	£4,690	NIPT PP2

Analysis	Total		*vs* No test and RAADP (current practice)	*vs* next best strategy	
	Cost	QALYs	ICER	ICER	Comparator
NIPT PP2	£15,252,345	2,433,755	£35,021	---	---
NIPT PP3	£15,438,716	2,433,773	£970,788	---	---
NIPT PP4	£15,350,383	2,433,755	£29,909	---	---
SA4 - Uptake with RAADP (with and without high-throughput NIPT performed)					
Uptake of RAADP at 87.5%					
No test and RAADP	£16,060,984	2,433,733	---	£1,430,198	NIPT PP1
NIPT PP1	£15,477,810	2,433,733	£1,430,198	£4,691	NIPT PP2
NIPT PP2	£15,390,257	2,433,714	£35,171	---	---
NIPT PP3	£15,576,545	2,433,733	£1,188,057	---	---
NIPT PP4	£15,488,218	2,433,714	£30,035	---	---
Uptake of post-partum anti-D immunoglobulin at 91.6%					
No test and RAADP	£16,029,705	2,433,743	---	£1,360,214	NIPT PP1
NIPT PP1	£15,446,384	2,433,742	£1,360,214	£4,691	NIPT PP2
NIPT PP2	£15,358,829	2,433,724	£35,137	---	---
NIPT PP3	£15,545,127	2,433,742	£1,129,960	---	---
NIPT PP4	£15,456,798	2,433,724	£30,006	---	---
Uptake of RAADP at 87.5% and post-partum anti-D immunoglobulin at 91.6%					

Analysis	Total		*vs* No test and RAADP (current practice)	*vs* next best strategy	
	Cost	**QALYs**	**ICER**	**ICER**	**Comparator**
No test and RAADP	£16,101,601	2,433,721	---	£1,532,578	NIPT PP1
NIPT PP1	£15,518,619	2,433,721	£1,532,578	£4,692	NIPT PP2
NIPT PP2	£15,431,068	2,433,702	£35,216	---	---
NIPT PP3	£15,617,343	2,433,721	£1,273,046	---	---
NIPT PP4	£15,529,017	2,433,702	£30,072	---	---
SA5 – High-throughput NIPT inconclusive results rate					
Please see section above on SA5					
SA6 – Cost of high-throughput NIPT and anti-D immunoglobulin					
Please see section above on SA6					
SA7 – Cost of fetal-maternal haemorrhage test					
No test and RAADP	£8,132,446	2,433,756	---	£621,464	NIPT PP3
NIPT PP1	£7,986,460	2,433,756	£317,485	---	---
NIPT PP2	£7,915,559	2,433,737	£11,340	---	---
NIPT PP3	£7,846,683	2,433,756	£621,464	£3,809	NIPT PP4
NIPT PP4	£7,775,584	2,433,737	£18,658	---	---
SA8 – Post-partum management of high-throughput NIPT inconclusive results					
Please see section above on SA8					

6.6 Discussion of the independent economic assessment

The evidence to support the diagnostic accuracy of the NIPT is of good quality. We can combine this with established evidence for the efficacy of RAADP and post-partum anti-D

immunoglobulin in order to estimate the impact of introducing NIPT testing on the number of sensitisations. However, there is little evidence as to the impact of sensitisations in terms of their long term health and cost consequences. Our model suggests that each additional sensitisation costs the NHS £3,167 and is associated with a loss of approximately 0.9 QALYs, but these estimates are subject to uncertainty and incorporate expert opinion.

There exists uncertainty regarding the cost of introducing the high-throughput NIPT. The unit cost will vary with throughput, and may be subject to an additional royalty fee. Unless the NIPT can be incorporated seamlessly into routine antenatal care, it may result in additional costs for blood draw, transport of samples, and antenatal care visits to administer the test and deliver counselling and results. We conducted extensive sensitivity analysis to address this uncertainty and to identify the threshold cost per NIPT. The cost of high-throughput NIPT has to increase by only [redacted] above that modelled in the base case in order for No test and RAADP to be the preferred strategy. The unit cost of high-throughput NIPT to the NHS is the most important parameter in determining the cost-effectiveness. While there is uncertainty as to the timing of the test, our analysis suggests that this is not influential in determining the cost-effectiveness results either in terms of diagnostic accuracy or in terms of the extent of management costs for potentially sensitising events that can be avoided.

As might be expected, the potential net health benefits of using the NIPT to target care are reduced as the rate of inconclusive results is increased. However, our sensitivity analysis indicates that even with high-throughput NIPT inconclusive results as high as 14.3% the introduction of NIPT compares favourably to current practice. The ability of the NIPT result to avoid unnecessary use of anti-D immunoglobulin varies systematically according to ethnicity. While this may not be an equality issue, it should be noted that following the introduction of NIPT any unnecessary use of anti-D immunoglobulin will be proportionately higher in ethnic groups such as those of African origin. We can conclude that the identification of the false positive results is key to the estimation of the cost-effectiveness outcomes, negatively impacting the results if this rate is higher, and altering the post-partum strategy that would offer the highest net health benefit.

There a numerous ways in which the results of the high-throughput NIPT could be used to guide post-partum testing and administration of anti-D immunoglobulin. We have compared four alternative post-partum scenarios, and the results indicate that cord serology testing should be retained in women for whom the NIPT indicates a RhD-negative fetus. This use of cord serology to capture false negative results has the potential to undermine the implementation of the test if it impacts on the confidence in the NIPT results. A post-partum

strategy that distinguishes between inconclusive results and positive results offers the greatest cost-savings.

If the cost of fetal-maternal haemorrhage test is high relative to cord serology, then it would make sense to apply cord serology to women with positive and inconclusive NIPT results. This allows for the low cost cord serology test to avoid both the unnecessary use of a much more expensive fetal-maternal haemorrhage test and unnecessary post-partum anti-D immunoglobulin. It is likely that these benefits are almost entirely obtained by applying cord serology in women with inconclusive results as 30-40% of these would be revealed to be carrying a RhD-negative fetus. In contrast where the results of the NIPT indicate a RhD-positive fetus the rate of false positives is very low. In the base case analysis women who receive inconclusive results are managed as if they test positive, but there may be potential for further cost savings if these are treated as a distinct group in terms of post-partum care. This would allow for a post-partum scenario where cord serology was applied to women who test negative and to those who test inconclusive, but where fetal-maternal haemorrhage tests and anti-D immunoglobulin is provided without cord serology in women who test positive.

6.7 Conclusions of the cost-effectiveness section

The use of high-throughput NIPT to guide the provision of anti-D immunoglobulin prophylaxis is estimated to be cost saving compared to current practice of providing RAADP to all women who are RhD-negative. The extent of the cost saving is highly sensitive to the cost of the NIPT itself to the NHS, which comprises the base unit cost per test, the level of any royalty fee, and any increase in antenatal care costs required to accommodate an additional test. In the base case analysis the extent of the cost-saving is sufficient to outweigh the small increase in sensitisations and the associated small QALY loss through using NIPT. However, even a small increase in the cost imposed on the NHS of [redacted] or more per test would cause the ICER for No test and RAADP to reduce below £20,000 per QALY.

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Three non-comparative studies (Soothill 2014, Banch Clausen 2014, Grande 2013) reported outcome measures relating to anti-D doses administrated. All studies found that the use of NIPT reduced the total use of anti-D Ig doses, particularly decreasing by 29% in one UK study by Soothill et al., because around 35% of RhD-negative women avoided unnecessary anti-D administration.

Four studies reported moderate to high compliance with antenatal anti-D Ig administration. The compliance with antenatal anti-D administration after a positive NIPT result ranged from 86% to 96.1% (four studies). High-throughput NIPT testing uptake rates ranged from 70% to over 95% (seven studies).

The results from the simulation study suggested that the use of NIPT testing to determine antenatal anti-D use would substantially reduce the number of women receiving anti-D unnecessarily, from 38.9% to 5.7%. Results were sensitive to the rate of compliance. NIPT use could increase sensitisation rates by up to 15 sensitisations per 100,000 women if postpartum cord blood testing is continued, or 28 per 100,000 women if cord blood testing is withdrawn and postpartum anti-D given on the basis of the NIPT result. Sensitisation rates are minimised by ensuring women who do not receive an NIPT test are still offered, and receive, antenatal anti-D. The results suggest that NIPT test results (if available and conclusive) could potentially be used in place of cord blood testing for administration of postpartum anti-D, if the small increase in sensitisations rates can be considered ethically acceptable.

7.1.3 Implementation

Twelves studies were included in the review of implementation. Most of the included studies were large cohort studies reporting implementation data alongside with diagnostic accuracy data, while one study was a survey based at the UK (London). All the large cohort studies reported high diagnostic accuracy of high-throughput NIPT and suggested that high throughput RhD genotyping of foetuses in all RhD negative women was feasible and should be recommended. A number of studies reported potential issues of implementation such as those relating to programme anti-D prophylaxis compliance. Some studies highlighted the importance of short transport times of samples and the need for effective management of transporting samples. Some studies also identified the need for greater knowledge of NIPT testing among physicians and midwives.

A UK-based survey (Oxenford 2013) revealed that, while most of the women surveyed supported the implementation of NIPT testing, their current knowledge of Rhesus blood groups and anti-D administration was limited, which could be a barrier to implementation.

7.1.4 Cost effectiveness

Seven cost-effectiveness studies were included in the review. Conflicting results were identified across the existing economic studies with 3 of the studies reporting that NIPT fetal RhD genotyping did not appear cost-effective. The unit cost of the test was consistently identified as a key driver of the cost-effectiveness results and the potential for the use of NIPT to result in overall cost savings. Only 1 of the studies was undertaken in a UK context but this study did not explicitly explore how the introduction of NIPT could impact on costs relating to potentially sensitising events. Of the studies undertaken outside the UK, differences in health care systems and implementation of anti-D immunoglobulin policies limit their relevance to UK practice. In conclusion, none of the existing studies were considered to be sufficiently generalisable to inform the specific the decision problem as set out in the NICE scope for the current assessment.

A *de-novo* independent economic model was developed to assess the cost-effectiveness of high throughput NIPT to identify fetal Rhesus D status in women who are RhD-negative and not known to be sensitised to the RhD antigen. The model was made up of two main elements: (1) an identification part reflecting the diagnostic performance and costs of the alternative identification strategies; and (2) a treatment part that evaluated the subsequent costs and outcomes (expressed in QALYs) of alternative care pathways. Four alternative ways in which the use of high-throughput NIPT may impact on the existing post-partum care pathway were evaluated (cord serology, fetal-maternal haemorrhage testing and post-partum anti-D immunoglobulin). These included scenarios in which the result of the NIPT was only used to guide RAADP only (with all women continuing to receive cord serology with fetal-maternal haemorrhage testing and post-partum anti-D immunoglobulin as required, irrespective of NIPT test result) and scenarios where the NIPT result guided both RAADP and separate aspects of post-partum care. A series of additional sensitivity and scenario analyses were also performed.

Our *de-novo* economic model indicated that the use of high-throughput NIPT to guide the prenatal and post-partum provision of anti-D immunoglobulin prophylaxis is estimated to be cost saving compared to current practice of providing RAADP to all women who are RhD-negative. The magnitude of the cost saving appears highly sensitive to the cost of the NIPT itself to the NHS, which comprises the base unit cost per test, the level of any royalty fee, and

any increase in antenatal care costs required to accommodate an additional test. In the base case analysis the extent of the cost-saving appears sufficient to outweigh the small increase in sensitisations and the associated small QALY loss through using NIPT compared to current practice. However, even a small increase in the cost imposed on the NHS of [redacted] or more per test would alter these conclusions.

In the base-case analysis, all four separate post-partum scenarios were estimated to be cost saving but also less effective than current practice. Based on a cross section of 100,000 pregnancies, the magnitude of cost savings varied between approximately £485,000 and £671,000. The magnitude of the QALY loss varied between 0.5 QALYs and 19.1 QALYs (per 100,000 pregnancies). Although the magnitude of the cost-savings was sufficient to outweigh the associated QALY loss when each post-partum scenario was separately compared to current practice, these four separate scenarios potentially represent separate and distinct testing and management strategies that should be directly compared. In the base-case analysis, the strategy in which the NIPT result is used to guide RAADP only (i.e. all women continuing to receive cord serology with fetal-maternal haemorrhage testing and post-partum anti-D immunoglobulin) was associated with the highest NHB and had the highest probability of being cost-effective for threshold values of £20,000 and £30,000 per QALY (probability of 0.65 and 0.73, respectively). However, the use of cord serology to capture false negative results has the potential to undermine the implementation of the test if it impacts on the confidence in the NIPT results. The most efficient post-partum strategy was also shown to vary across several of the main sensitivity analysis.

A post-partum strategy that distinguishes between inconclusive results and positive results offers the greatest cost-savings. In the base case analysis women who receive inconclusive results were assumed to be managed as if they test positive, but there may be potential for further cost savings if these are treated as a distinct group in terms of post-partum care. This could allow for a post-partum scenario where cord serology was applied to women who test negative and to those who test inconclusive, but where fetal-maternal haemorrhage tests and anti-D immunoglobulin is provided without cord serology in women who test positive.

7.2 Strengths and limitations of the assessment

7.2.1 Clinical effectiveness

Extensive literature searches were conducted with an attempt to maximise retrieval of potentially relevant studies. These included electronic searches of a variety of bibliographic databases as well as screening of clinical trial registers and conference

proceedings to identify unpublished studies. The search strategy did not restrict by study design. The review process followed recommended methods to minimise the potential for error and/or bias. The quality of the included studies was assessed and accounted for when interpreting the review results. Appropriate synthesis methods were employed by taking into account the heterogeneity of study characteristics.

For limitations, only studies in English were included, therefore some potentially relevant non-English language studies may have been missed. There was very limited evidence relating to the clinical effectiveness of high-throughput NIPT testing. No studies were identified reporting adverse effects of high-throughput NIPT testing. There was some evidence of inconsistency in the meta-analysis of diagnostic accuracy studies. The observed heterogeneity may be explained by variations in methods used in the high-throughput NIPT approach (including diagnostic accuracy thresholds, and number and types of exons targeted), gestational age at the time of testing, and different methods of

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handling inconclusive test results. There were also variations in the reporting of included studies. Particularly, two studies (Akolekar and Thurik) did not report the number of inconclusive results of the test and some studies did not report detailed reasons for inconclusive results.

7.2.2 Cost effectiveness

The *de-novo* economic model was specifically developed to address the limitations of existing studies and concerns regarding the generalisability to current UK practice. The main strength of the decision model is the linkage between the diagnostic accuracy of a given identification strategy, the impact on subsequent treatment decisions and the ultimate effect on health outcomes and costs. A key element of the model is based on the previous economic model underpinning NICE TA 156 on RAADP ensuring consistency between the separate diagnostic and technology appraisals. A broad range of scenario and sensitivity analyses were undertaken to address key assumptions and uncertainties.

7.3 Uncertainties

7.3.1 Clinical effectiveness

In this assessment we identified very limited data on the evaluation of clinical effectiveness for using high-throughput NIPT testing to detect fetal RhD status in RhD negative women. Therefore, the potential role of high-throughput NIPT testing in terms of its clinical impact on the care pathway and adverse effects to the mother and fetus remains unclear. In particular, we did not identify any studies reporting comparative data relating to patient-related outcomes such as quality of life measure.

Due to a lack of sufficient data from included studies, we were unable to conduct subgroup analyses based on ethnicity. Therefore, whether the diagnostic performance of high-throughput NIPT testing differs between different ethnic groups remains unclear.

In terms of implementing high-throughput NIPT testing in healthcare settings, no studies were identified reporting compliance rates to prenatal anti-D treatment in the UK settings. Although a few non-UK studies reported compliance rates to prenatal anti-D treatment, the generalisability of their findings to the UK settings remains uncertain due to variations in national guidelines and health policies between different countries.

7.3.2 Cost effectiveness

There exists uncertainty regarding the cost of introducing the high-throughput NIPT. The unit cost will vary with throughput, and may be subject to an additional royalty fee. Unless the NIPT can be incorporated seamlessly into routine antenatal care, it may result in additional costs for blood draw, transport of samples, and antenatal care visits to administer the test and deliver counselling and results. We conducted extensive sensitivity analysis to address this uncertainty and to identify the threshold cost per NIPT. The cost of high-throughput NIPT has to increase by only [redacted] above that modelled in the base case in order for current practice to be the preferred strategy.

While there remains uncertainty as to the timing of the test, our analysis suggests that this does not appear influential in determining the cost-effectiveness results either in terms of diagnostic accuracy or in terms of the extent of management costs for potentially sensitising events that can be avoided.

Although the evidence to support the diagnostic accuracy of the NIPT is of good quality, existing evidence informing the impact of sensitisations in terms of their long term health and cost consequences are more limited and highly uncertain.

7.4 Other relevant factors

Due to a lack of relevant evidence, we have not considered any adverse health impacts from provision of a blood based product. While widespread global use of anti-D immunoglobulin would suggest that is it safe, there remains uncertainty as to the potential for risk associated with prion disease or other unknown pathogens. There may also be ethical considerations concerning the unnecessary administration of a blood-based product.

We also have not considered any adverse consequences from the introduction of the high-throughput NIPT over and above the slight increase in risk of sensitisation. Women who know they are sensitised may factor this into their family planning decisions, but we have assumed no such impact within the model. It is possible that the NIPT could inadvertently reveal mistaken paternity of the child in cases where a woman's partner knows that he is RhD-negative and the baby is revealed to be RhD-positive. Concerns about revealed paternity have been noted in relation to testing the father's blood type in order to target anti-D immunoglobulin only to those women with RhD-positive partners. The inclusion of an additional pre-natal test could potentially have adverse impacts on uptake of other antenatal care if the overall quality of care is compromised by the additional test burden.