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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
International Blood Reference Group Laboratory, (NHSBT)	1.	P11	Glossary	The definitions of false positive and false negative are not suitable for this setting as neither expressing nor not expressing the D antigen is a disease	These will be corrected to avoid reference to "disease".
International Blood Reference Group Laboratory, (NHSBT)	2	P13	Abstract	I don't think PSS is defined prior to appearing in the second paragraph of methods	The abbreviation will be replaced with "personal social services".
International Blood Reference Group Laboratory, (NHSBT)	3	P13	Abstract	Results second line "twelves" should be twelve	This will be corrected.
International Blood Reference Group Laboratory, (NHSBT)	4	P16 (and throughout)	Background	Having stated RhD at the beginning I think that D can be used (D positive, D negative, anti-D etc) For both simplicity and compliance with common nomenclature	The term "RhD positive/negative" is the more common nomenclature in the included studies, and we think just using "D" might be unclear. No changes made. "Anti-RhD" will be corrected to "anti-D" where it occurs.
International Blood	5	P21	1.4.4	In the first paragraph I think that "guide RAADP only" may be misleading as it also guides provision of anti-D	Thank you for your comment. That is correct. It may also guide the provision of anti-D for

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Reference Group Laboratory, (NHSBT)				for potentially sensitising events. In the third paragraph it states that the timing of the test does not influence cost effectiveness. Later text suggests that earlier administration saves more anti-D for sensitising events.	potentially sensitising events. We are happy to rephrase this to: "In the base-case analysis, the strategy in which the NIPT result is used to guide RAADP and potentially sensitising events (…) had the highest probability of being cost-effective."
International Blood Reference Group Laboratory, (NHSBT)	6	P26	2.3.1	Second paragraph *RHD* should be in italics. Where the gene is discussed throughout the text it should be in capitals and italics *RHD*	We will correct report to use *RHD* when referring to the gene.
International Blood Reference Group Laboratory, (NHSBT)	7	P27	2.3.2 & throughout	"NIPT tests", "NIPT test", "NIPT testing" and "NIPT screening" ie "non-invasive pre-natal testing testing" etc can all be removed just leaving NIPT (usually deleting prefixes such as "an..", "the….").	Thank you for your comment. This will be revised in a future version of the report. . However in some places "NIPT test" may be retained for ease of reading, even if not technically correct.
International Blood Reference Group Laboratory, (NHSBT)	8	P28	2.3.4	NHSBT isn't a company it is an NHS organisation	We used company in the NICE nomenclature to refer to the group that will provide the diagnostic technology under assessment. To avoid confusion with a business entity we can amend the wording to NHS organisation.
International Blood Reference	9	P73	4.3.3	"Twelves"	This will be corrected.

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Group Laboratory, (NHSBT)					
International Blood Reference Group Laboratory, (NHSBT)	10	P106	6.3.9	Second paragraph last but one line should be “haemolytic”	Not a factual inaccuracy. No comments.
International Blood Reference Group Laboratory, (NHSBT)	11	P108	6.3.12	The value quoted by Szczepura for Kleihauer is incorrect. The Kleihauer is a very labour intensive test requiring skill and time from the operator. A local Trust charges £25 for this test and I suspect that activity based costing may come up with a higher value. I think Szczepura et al may have applied the cost of blood group serology. Using such a low figure I think will misrepresent the true cost.	In the base case analysis we used a price of £128.10. The price as published by Szczepura was used in a sensitivity analysis.
International Blood Reference Group Laboratory, (NHSBT)	12	P122		Second paragraph. The following statement should probably be removed “Strategies with more sensitisation have marginally less test cost as sensitised women do not receive NIPT to guide RAADP in subsequent pregnancies (however it is worth noting that NIPT is recommended to be used in women who are sensitised in order to guide antenatal care)” This doesn’t really fit. NIPT is performed using a more expensive method in sensitised women and as you state being sensitised increases the cost of care	Not a factual inaccuracy. No comments.

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				generally. Despite the caveat in brackets I think the statement is potentially misleading.	
International Blood Reference Group Laboratory, (NHSBT)	13	P124		Second paragraph: There is an assumption regarding cord blood accuracy (tests are typically performed manually and there can be maternal / cord sample mix up). It has been used as the “gold standard” for NIPT in this setting but is error prone itself	Not a factual inaccuracy. We will add a comment on the potential imperfections of cord bold testing as a reference standard to the final version.
International Blood Reference Group Laboratory, (NHSBT)	14	P127	6.5.2.2	There is no plausible explanation for the minor differences in false negative and false positive rate after 11 weeks gestation other than chance. On that basis the things that would influence cost effectiveness most would be a) not having to make a special visit for the test as that would significantly increase costs over having the test in conjunction with a current point of contact in the care pathway (favouring antenatal ultrasound or Downs screening visits) b) The number of sensitising events for which anti-D could be avoided (favouring the earliest time point) Any suggestion that it may be cheaper as a result of an appearance of a small variance in accuracy (as a result of random chance) may divert from a and b	Not a factual inaccuracy. No comments.
International Blood	15	129	6.5.2.4	It would seem plausible that knowing the fetal type would lead to better compliance with anti-D in those	Not a factual inaccuracy. No comments.

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Reference Group Laboratory, (NHSBT)				carrying a D positive fetus. I believe one of the European teams who have implemented this may have shown this but cannot find a reference unfortunately.	
International Blood Reference Group Laboratory, (NHSBT)	16	134	Fig 18	This seems to be missing from my version	Not a factual inaccuracy. No comments.
International Blood Reference Group Laboratory, (NHSBT)	17	135	6.5.2.7	The value quoted by Szczepura for Kleihauer is incorrect. The Kleihauer is a very labour intensive test requiring skill and time from the operator. A local Trust charges £25 for this test and I suspect that activity based costing may come up with a higher value. I think Szczepura et al may have applied the cost of blood group serology. Using such a low figure I think will misrepresent the true cost.	See comment 11.
International Blood Reference Group Laboratory, (NHSBT)	18		Response to email from NICE	[redacted]	We have not removed any highlighting of commercial-in-confidence information.

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Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				[redacted]	
International Blood Reference Group Laboratory, (NHSBT)	19	14	Abstract and general comment		Not a factual inaccuracy. No comments.
International Blood Reference Group Laboratory, (NHSBT)	20	21	1.4.4 Cost effective ness		Not a factual inaccuracy comment. No comments.
International Blood Reference	21	27	2.3.4 Anticipat ed costs		Please see reply to comment 18.

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Group Laboratory, (NHSBT)			associated with technology	[redacted]	
International Blood Reference Group Laboratory, (NHSBT)	22	107	6.3.10 Cost of high-throughput NIPT		Not a factual inaccuracy. No comments.
International Blood Reference Group Laboratory, (NHSBT)	23	118 and 134	Table 25 and 6.5.2.6 Sensitivity analysis on NIPT and Anti-		We apologise that a suggested [redacted] figure was not redacted in Table 25 and page 134. We will redact in future versions of the report, but note that these statements did not suggest that [redacted] was a figure provided to us by any organisation.

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			D costs		
Scottish National Blood Transfusion Service	24	13 19	Results section 1.4.1	The eight studies included in the meta-analyses carried out NIPT at different gestation periods – unclear whether their results should be pooled as the false negative/positive rate varies with gestation age	We consider the meta-analysis necessary to summarise the typical diagnostic accuracy of NIPT (which may not be used at a consistent time). These meta-analyses are based on tests conducted after 11 weeks' gestation, after which time there was no evidence of variation in diagnostic accuracy. The impact of gestational age was investigated fully (see Section 4.2.2.5).
Scottish National Blood Transfusion Service	25	14 140 143	2nd paragraph 6.7 7.1.4	The document does not analyse the cost, medical and emotional impact of the increased sensitisations; further the current cost for the NIPT does not include the increased cost from need to transport samples significant distances and the likely extra clinic appointments – the savings indicated by introducing NIPT are highly dependent on the cost of the NIPT – once the above are also taken into account it is unlikely that the cost savings indicated will be real and given NIPT is clinically inferior to the current management it does not make clinical or financial sense to move to NIPT.	The cost effectiveness analysis incorporates the cost and medical impact of sensitisations. The report is clear in stating that transportation costs have not been included in the economic analysis (for instance on section 6.6, page 138). However a threshold analysis over the price of the diagnostic test was done which informs the impact of any additional related costs, including the transportation of blood samples.
Scottish National Blood Transfusion	26	14	Conclusions	Are the cost savings of £296K-£409K per 100,000 pregnancies referring to all pregnancies or just RhD negative pregnancies – the implications would be significantly different.	Pregnancies in women who are RhD negative, which are the target population for this intervention.

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Service					
Scottish National Blood Transfusion Service	27	16 121	1.1 6.5.1	Potential risk associated with administration of anti-D has not been quantified. "…global use of anti-D immunoglobulin has yet to produce evidence for any adverse consequences" This is important when considering whether to change current effective practice with RAADP (a safe product) to NIPT which is clinically inferior.	Not a factual inaccuracy. We found that NIPT is clinically and cost effective even if anti-D is perfectly safe (as is assumed in all analyses) If there is a risk with anti-D use that would be in favour of NIPT. We found no evidence on risks of anti-D administration, so cannot comment further.
Scottish National Blood Transfusion Service	28	19 56 72	1.4.2 Sensitisations 4.3.2	The comparison with historical controls where the routine management was postpartum anti-D only is not relevant to the UK as the current routine practice in the UK involves both RAADP and post-partum anti-D so the risk reduction in sensitisation with NIPT may not be significant in the UK	We agree, but we are only here reporting the findings of (limited) relevant papers. The simulation (Section 4.2.4) and the cost-effectiveness analyses give a fair comparison.
Scottish National Blood Transfusion Service	29	20 72	1.4.2 4.3.2	While the additional sensitisations at first glance appear few compared to the underlying rate of sensitisation with antenatal anti-D they are nevertheless an increase in the number of sensitisations. Sensitisations due to the failure of anti-D will continue to occur whether using the current method of management or using NIPT as these are due to a failure of anti-D administration per se. Increasing the rate of sensitisations should be avoided if possible. There has not been any account taken of the impact of the increased sensitisation rate both on the women themselves who will not be able to have	The use of NIPT must increase the rate of sensitisation compared to universal anti-D use. The question is whether the increase is ethically acceptable and cost-effective. The simulation study in section 4.2.4 summarises what the increase in sensitisation rate would be. As is stated in that section, whether this increase is acceptable depends on ethical considerations (beyond the scope of the report) and costs (considered in the cost-

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		139	6.6	future low risk pregnancies and indeed in severe cases may end up not being able to have future healthy children and on the long term consequences to any children born with disability in the case of severe HDN. Withdrawing cord blood testing removes the last chance available to confirm the requirement for anti-D prophylaxis or not and therefore removes the chance to avoid sensitisation. Suggest that cord blood testing should be retained. "…cord serology testing should be retained in women for whom the NIPT indicates a RhD negative fetus." Given this then there will be no savings from removing the cord blood serology testing.	effectiveness analyses). The long term consequences to any children born with disability as a consequence of HDN are incorporated in the cost effectiveness analysis.
Scottish National Blood Transfusion Service	30	21 23 23 107 134 139	1.4.4 1.6.2 1.6.3 6.3.10 6.5.2.4 6.6	"NIPT appears cost saving but also less effective than current practice" – it is likely that once the need for extra transport/clinic appointments and the cost impact of the extra sensitisations is taken into account that the small amount of cost saving being predicted will be lost while at the same time introducing a less effective clinical practice.	Not a factual inaccuracy. No comments.
Scottish National Blood Transfusion Service	31	21	1.4.4 last paragraph	"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…." Unclear how this can be true given that the false negative/positive rate of the test varies with gestation.	The false positive rate does not vary with gestation. The false negative rate is higher before 11 weeks, but does not vary thereafter (see Figures 6-8). The cited section of the report refers only to post-11 weeks' testing.

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Scottish National Blood Transfusion Service	32	21	1.5.1	Given no studies have compared NIPT testing to universal administration of antenatal anti-D (current UK practice) it is difficult to extrapolate findings to the UK.	Not a factual inaccuracy. No comments.
Scottish National Blood Transfusion Service	33	21 23 42 54 84 139	1.5.1 1.6.3 4.2.2.1 4.2.2.5 5.2.3.1 6.6	The UK has a significant ethnic mix so the fact that NIPT may be much less specific in ethnic minorities is of concern. "Any diagnostic analysis of non-white ethnicities may therefore not give reliable results" – this will be a significant number of pregnancies in the UK – would there need to be a different management protocol for such patients? "None of the studies considered the effectiveness and/or cost effectiveness of NIPT in ethnic minority groups".	Not a factual inaccuracy. We cannot comment further, given the lack of data on non-white populations. Not a factual inaccuracy. No comments.
Scottish National Blood Transfusion Service	34	25 27 45	2.2 2.3.2 4.2.2.3	Current recommendation in the UK from the Royal College of Obstetricians and Gynaecologists is that women should have their booking appointment by 10 weeks gestation – given the data presented this would be too early for the NIPT to be included in the booking appointment.	Not a factual inaccuracy. This section is discussing current practice, not making recommendations about when NIPT could be used.
Scottish National Blood Transfusion Service	35	27	2.3.3	The cost savings predicted are based on the assumption that all NIPT will be carried out in one lab in England – this will require co-ordination and samples to be sent significant distances which will necessarily introduce a delay to processing these	Not a factual inaccuracy. Potential issues relating to sample stability and transportation, as far as they have been reported in the literature, are discussed in

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		73	4.3.3	samples. There is no data presented as to how long the cffDNA is stable for and therefore the acceptable timelines for processing these samples to ensure valid results. "Some studies emphasised the importance of short transport times of samples and the need for good management of transporting samples." Further adding the need to send an extra blood sample to a centralised lab in the UK and waiting for the results from this sample to be relayed back to the requesting clinic will add an extra layer of complexity to the management of RhD negative pregnancies – due to the process that would be required it is highly likely that a number of samples would be lot in transit or delayed and need repeating – this may lead to some RhD negative women missing out on prophylaxis with anti-D and is likely to further increase the cost of introducing NIPT when compared to the current management of RhD negative pregnancies.	Section 4.2.5.
Scottish National Blood Transfusion Service	36	33	4.1.2.3	""High-throughput" is a subjective concept and there is no clear consensus on its definition" – this suggests that the studies being compared may have used different techniques and therefore may not be easily comparable.	We simply noted that "High-throughput" is not formally or precisely defined. We created a definition for this review as described in Section 4.1.2.3. We therefore consider the NIPT techniques used in the included studies to be sufficiently similar for comparison. We excluded many studies where the machine did not meet the definition of high-

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					throughput for this review.
Scottish National Blood Transfusion Service	37	43	4.2.2.2	"…prediction algorithm was judged daily and adjusted as needed" – given the potential implications of a false negative then this would be a cause for concern.	Not a factual inaccuracy. Nor is it a justification for excluding the study.
Scottish National Blood Transfusion Service	38	50	4.2.2.4	The considerable unexplained variation even in studies where tests were all conducted in Bristol using the same test is of concern.	Not a factual inaccuracy. We agree, but this is a point to be put to NHSBT. We cannot comment further without evidence.
Scottish National Blood Transfusion Service	39	56 117	NIPT Uptake SA5	There is no comment on whether the women who consented to receive RhD genotyping were happy to have their management based on the result – were some of them keen to have anti-D prophylaxis anyway in the presence of a negative result just in case?	This does not appear to be the case. See Table 9 row 5.
Scottish National Blood Transfusion Service	40	61	4.2.4	Introducing NIPT doubles the number of women who miss out on potentially beneficial prophylaxis from 0.6% to 1.2% - the savings from introducing NIPT need to be significant to justify this.	Whether cost savings justify this is incorporated into the economic analyses.
Scottish National Blood Transfusion Service	41	64 71 71	4.2.5.2 4.2.5.2 4.3.1	"…high throughput RhD genotyping….was feasible" – at what gestation? "NIPT testing could be carried out at any time between 25 and 28 weeks" – this is likely to be too late to allow savings to be made. "Hence NIPT cannot be recommended before the 2nd	Not a factual inaccuracy This is a general comment, not specific to any timing. Current practice is to offer anti-D at around 28-30 weeks. This is compatible with NIPT at

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				trimester, and may be best performed later in the second trimester" – again likely to be too late.	25-28 weeks
Scottish National Blood Transfusion Service	42	71	4.3.1	"…reduce the false positive rate by further targeted testing of women with an initially inconclusive result" – the need for this is very likely to result in no savings being made and further increases the complexity?	Not a factual inaccuracy. This is a clinical efficacy comment as to how handle inconclusive tests. It may increase costs, but how much would be speculative. The cost-effectiveness analysis assumes current practice of no further testing.
Scottish National Blood Transfusion Service	43	77	5.2.2	"Most studies considered the introduction of NIPT at a single time point, usually at first routine antenatal care appointment occurring between 8-12 weeks' gestation" – from the rest of the data presented in the document this would be too early for reliable results.	Not a factual inaccuracy. No comments.
Scottish National Blood Transfusion Service	44	85	5.2.3.3	"..NIPT…in the 1st trimester was a cost-reduction strategy in comparison to performing the test later in pregnancy" – given the data presented that the test is only reliable when done after 11 weeks gestation then the savings predicted, particularly when take into account transport etc are likely not to be realised.	Not a factual inaccuracy. No comments.
Scottish National Blood Transfusion Service	45	87	5.2.4	"…implementation of NIPT in the clinical pathway of the RhD negative woman was not expected to produce important clinical benefits".	Not a factual inaccuracy. No comments.
Scottish National Blood	46	88	5.2.4	"…targeting of RAADP based on immunological RhD typing of the father is cost-effective compared to the use of NIPT". This should be considered when	Not a factual inaccuracy. No comments.

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Transfusion Service				deciding whether to replace the current system with NIPT.	
Scottish National Blood Transfusion Service	47	94	6.2.1	"..assume the consequences of sensitisation do not affect the pregnancy in which it occurs" – infrequent but some babies are infact affected in the index pregnancy as also mentioned at an earlier time point in the document itself (Pg 56).	Not a factual inaccuracy. No comments.
Scottish National Blood Transfusion Service	48	108	6.3.13	The estimated annual costs for minor and major development problems appear an underestimate – if a child has major development problems it is hard to see how this would only cost £574 per year? Also the average cost per sensitisation being estimated to be £3167 seems an underestimate given these pregnancies will need many more clinic appointments, MCA dopplers at regular intervals and potentially in utero transfusions?	The average costs relating to sensitisations were based on the previous NICE appraisal of RAADP as no other sources of evidence were identified to inform these. The health resource consumption underlying these annual costs for both the management of maternal and neonatal sensitisation have been confirmed by clinical experts as stated in section 6.3.13, page 108.
Scottish National Blood Transfusion Service	49	114	6.4	"The introduction of the high-throughput NIPT is not expected to produce large difference in clinical outcomes, and may result in lower health outcomes compared to RAADP if the rate of sensitisations is increased" – this is important.	Not a factual inaccuracy. No comments.
Scottish National Blood Transfusion Service	50	116	SA3	"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" – this may again have a negative impact on any potential savings.	Not a factual inaccuracy. No comments.
Scottish National	51	127	6.5.2.2	"..introduction of NIPT results in lower health benefits when compared to No test and RAADP. This happens	Not a factual inaccuracy. No comments.

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Blood Transfusion Service				irrespectively of the timing at which the test is carried out." – this is important.	
Scottish National Blood Transfusion Service	52	142	7.1.2	"NIPT use could increase sensitisation rate by up to 15 sensitisation per 100000 women if postpartum cord blood testing is continued or 28 per 100000 women if cord blood testing is withdrawn…" All previous estimates in the document quote 3-13 extra sensitisations – which is correct? Clearly if the correct rate of increased sensitisation is 15-28 per 100000 women then this is a bigger concern as the rate of increased sensitisation is significantly higher than quoted elsewhere in the document.	The 15-28 was based on Table 12, where women who do not receive NIPT also do not receive anti-D. The numbers in Section 7 will be corrected to reflect the main results in Table 11.
Scottish National Blood Transfusion Service	53	146	7.3.2	"…existing evidence informing the impact of sensitisations in terms of their long term health and cost consequences is more limited and highly uncertain" – this is important and if identified could significantly impact the conclusions that would be reached.	Not a factual inaccuracy. No comments.
Scottish National Blood Transfusion Service	54			SNBTS estimate that the net cost of introducing an NIPT programme in NHS Scotland using in-house testing would be in the order of £200,000 per annum rather than leading to savings – the predicted cost saving estimates in this document seem unlikely to be realised particularly as the predicted savings do not at present take into account the increased cost associated with the likely extra clinic appointments, the management of the extra sensitisations and the	Not a factual inaccuracy. No comments.

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				definite extra cost of transporting samples significant distances to get them to a centralised lab .	
Scottish National Blood Transfusion Service	55			Adding NIPT introduces another decision step into the maternal care pathway for RhD negative mothers – this will increase complexity with the additional risk of error. This should be considered carefully when introducing a service that is clinically inferior to current management.	Not a factual inaccuracy. No comments.
NHS England	56			There is little double that screening of all Rhesus negative women will reduce the need for unnecessary prophylaxis and therefore reduce costs on anti-D and the risks to the women (of blood born infection known or unknown). There is little double thought that NIPT screening will lead to a small false negative rate and thus the risk of fetal anaemia after alloimmunisation. It difficult to know how severe such alloimmunisation would be if it occurred and all such women would not require IUT as treatment. But there would be a significant cost to monitoring the pregnancy and potentially premature delivery (apart from the costs of IUT if required which is expensive and I believe under costed in the paper).	Not a factual inaccuracy. No comments.
NHS England	57		6.7	The cost of counselling if the NIPT test was to be universally undertaken would be significant but again would partially be incorporated into an existing screening midwife role.	Not a factual inaccuracy. No comments.
NHS England	58		6.7	I think the costs of counselling and management of those small number of pregnancies that are false	Not a factual inaccuracy. No comments.

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				negatives requires perhaps further evaluation	
NHS England	59		8	If it is less effect than current practice overall it's difficult to support. The 'headlines' would be damaging even if there were some cost savings.	Not a factual inaccuracy. No comments.
British Society for Haematology	60	All through the document	Terminology	The correct terminology for the Rh blood group system is Rh and not rhesus or Rhesus, and the correct terminology for the antigen is D, and not RhD. Wherever genes are referred to this should be in capitals and italics, e.g. *RHD*. Where anti-D is referred to it is not necessary to add 'antibodies' as in 'anti-D antibodies'. Incorrect terminology makes the document more difficult to read and it can sometimes change the meaning (see examples from page 26, below).	We will make corrections to the report in line with this comment.
British Society for Haematology	61	26	2.3.2	'African ethnicity, Rh-negative phenotype is mostly the result of genes that contain RhD sequences but do not produce D antigen (RHD-pseudogene).' The use of 'Rh' here instead of 'D' implies that these as Rhnull individuals.	This will be corrected.
British Society for Haematology	62	26	2.3.1	'In the UK, primers and probes for specific exons of the RHD gene are used, with a number of controls being tested (such as RhD positive DNA, RhD negative DNA, RHD pseudogene positive DNA, and no DNA).' These are all genes, but the use of RhD here suggests that they are antigens (which are not present in plasma).	This will be corrected.

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British Society for Haematology	63	78 - 157		Subheading of pages changes to 'TNF-alpha inhibitors for ankylosing spondylitis and nr-AxSpA' rather than 'High-throughput non-invasive prenatal testing for fetal RHD status'	This will be corrected.
British Society for Haematology	64	13 19	Results section 1.4.1	The eight studies included in the meta-analyses carried out NIPT at different gestation periods – unclear whether their results should be pooled as the false negative/positive rate varies with gestation age	See response to comment 24
British Society for Haematology	65	21	1.4.4 last paragraph	"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…." Unclear how this can be true given that the false negative/positive rate of the test varies with gestation.	Not a factual inaccuracy. No comments.
British Society for Haematology	66	44	4.2.2.3	With any test the 'accuracy' in practice will depend not only on the technical reliability of the test itself, but also on the effectiveness of procedures for correctly identifying women / samples being and transferring results between analysers and IT systems.	This is correct, but is innately accounted for because transfers of results would have happened in the studies. We note the importance of accurate transfer of results in Section 4.2.5.
British Society for Haematology	67	50	4.2.2.4	The considerable unexplained variation even in studies where tests were all conducted in Bristol using the same test is of some concern. Could this be due to different definitions of 'inconclusive' results in the three Bristol studies?	This must be addressed to NHS BT. We cannot comment.
British Society for Haematology	68	43	4.2.2.2	"…prediction algorithm was judged daily and adjusted as needed" – given the potential implications of a false negative then this would be a cause for concern (although this was not a study from the UK)	See response to comment 37

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British Society for Haematology	69	33	4.1.2.3	“”High-throughput” is a subjective concept and there is no clear consensus on its definition” – this suggests that the studies being compared may have used different techniques and therefore may not be easily comparable.	See response to comment 36
British Society for Haematology	70	16 121	1.1 6.5.1	“…global use of anti-D immunoglobulin has yet to produce evidence for any adverse consequences” Potential risk associated with administration of anti-D has not been quantified. However, it is accepted that there is always a potential risk in administering a blood product, and the ethics of this should be considered.	Not a factual inaccuracy. The report highlights the lack of evidence in this area at various points. We cannot comment further.
British Society for Haematology	71	21 23 42 54 84 139	1.5.1 1.6.3 4.2.2.1 4.2.2.5 5.2.3.1 6.6	The UK has a significant ethnic mix so the fact that NIPT may be less specific in ethnic minorities is of some concern. Would most of these would be false positive or inconclusive based on the test used in Bristol, or would there need to be a different management protocol for such patients? “Any diagnostic analysis of non-white ethnicities may therefore not give reliable results” – “None of the studies considered the effectiveness and/or cost effectiveness of NIPT in ethnic minority groups”.	See response to comment 33
British Society for Haematology	72	21 19 56	1.5.1 1.4.2 Sensitisations	Given no studies have compared NIPT testing to universal administration of antenatal anti-D (current UK practice) it is difficult to extrapolate findings to the UK.	Not a factual inaccuracy. No comments See also comment 32

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		72	4.3.2	The comparison with historical controls where the routine management was postpartum anti-D only is not relevant to the UK as the current routine practice in the UK involves both RAADP and post-partum anti-D so the risk reduction in sensitisation with NIPT may not be significant in the UK	
British Society for Haematology	73	142	7.1.2	"NIPT use could increase sensitisation rate by up to 15 sensitisation per 100000 women if postpartum cord blood testing is continued or 28 per 100000 women if cord blood testing is withdrawn…" All previous estimates in the document quote 3-13 extra sensitisations – which is correct?	See response to comment 52
British Society for Haematology	74	20 72	1.4.2 4.3.2	While the additional sensitisations appear few compared to the underlying rate of antenatal sensitisation to the D antigen, they are nevertheless an increase in the number of sensitisations. Sensitisations due to the failure of anti-D will continue to occur whether using the current method of management or using NIPT as we cannot do anything to influence that. Increasing the rate of sensitisations should be avoided if possible. There has not been any account taken of the impact of the increased sensitisation rate both on the women themselves who will not be able to have future low risk pregnancies and indeed in severe cases may end up not being able to have future healthy children and on the long term consequences to any children born with disability in the case of severe HDN.	See response to comment 29

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British Society for Haematology	75	94	6.2.1	"..assume the consequences of sensitisation do not affect the pregnancy in which it occurs" – infrequent but some babies are infact affected in the index pregnancy as also mentioned at an earlier time point in the document itself (Pg 56).	Not a factual inaccuracy. No comments.
British Society for Haematology	76	139	6.6	"…cord serology testing should be retained in women for whom the NIPT indicates a RhD negative fetus." Withdrawing cord blood testing removes the last chance available to confirm the requirement for anti-D prophylaxis, and D typing the cord sample at delivery should be retained for women predicted by NIPT to be carrying a D negative fetus, at least until the false negative rate for NIPT has been established in practice. The final error rate will depend on patient and sample identification, successful transmission of results across IT systems, and communication of results to the relevant people that can understand and act on them, as well as the inherent accuracy of the test.	Not a factual inaccuracy. No comments.
British Society for Haematology	77	14	Conclusions	Are the cost savings of £296K-£409K per 100,000 pregnancies referring to all pregnancies or just RhD negative pregnancies – as the implications would be significantly different.	See response to comment 26.
British Society for Haematology	78	87 114	5.2.4 6.4	"…implementation of NIPT in the clinical pathway of the RhD negative woman was not expected to produce important clinical benefits". "The introduction of the high-throughput NIPT is not expected to produce large difference in clinical	Not a factual inaccuracy. No comments.

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		127 61	6.5.2.2 4.2.4	outcomes, and may result in lower health outcomes compared to RAADP if the rate of sensitisations is increased" "..introduction of 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." These are important points Introducing NIPT doubles the number of women who miss out on potentially beneficial prophylaxis from 0.6% to 1.2% - the savings from introducing NIPT need to be significant to justify this (the ethics of giving an 'unnecessary' blood product should also be considered).	
British Society for Haematology	79	21 23 23 107 134 139	1.4.4 1.6.2 1.6.3 6.3.10 6.5.2.4 6.6	"NIPT appears cost saving but also less effective than current practice" – it is possible that once the need for extra transport/clinic appointments and the impact of the extra sensitisations is taken into account that the small amount of cost saving being predicted could be lost while at the same time introducing a less effective clinical practice.	See response to comment 30.
British Society for Haematology	80	27 73	2.3.3 4.3.3	The cost savings predicted are based on the assumption that all NIPT will be carried out in one lab in England – this will require co-ordination and samples to be sent significant distances which will necessarily introduce a delay to processing these samples. There is no data presented as to how long the cffDNA is stable for and therefore the acceptable	Not a factual inaccuracy. The issues around need for reliable transportation are discussed in Section 4.2.5.

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				timelines for processing these samples to ensure valid results. "Some studies emphasised the importance of short transport times of samples and the need for good management of transporting samples."	
British Society for Haematology	81	56 117	NIPT Uptake SA5	If not all women who consented to receive RhD genotyping were happy to have their management based on the result and some continued with RAADP in the presence of a negative result (e.g. 6% in Soothill study Table 9 page 58) this would increase costs.	Not a factual inaccuracy. No comments.
British Society for Haematology	82	77 85	5.2.2 5.2.3.3	"Most studies considered the introduction of NIPT at a single time point, usually at first routine antenatal care appointment occurring between 8-12 weeks' gestation" – from the rest of the data presented in the document this would be too early for reliable results. "..NIPT…in the 1st trimester was a cost-reduction strategy in comparison to performing the test later in pregnancy" – given the data presented that the test is only reliable when done after 11 weeks gestation then the savings predicted, particularly when take into account transport etc are likely not to be realised. Current recommendation in the UK from the Royal College of Obstetricians and Gynaecologists is that women should have their booking appointment by 10 weeks gestation – given the data presented this would be too early for the NIPT to be included in the booking appointment.	See response to comments 43, 44 and 34.

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British Society for Haematology	83	71 92	4.3.1 4.2.5.2	"Hence NIPT cannot be recommended before the 2nd trimester, and may be best performed later in the second trimester" "NIPT testing could be carried out at any time between 25 and 28 weeks" – this is may to be too late to allow savings to be made. It would seem sensible to combine NIPT testing with other antenatal appointments (16 week or the 18-20 weeks scan).	Not a factual inaccuracy. See also response to comment 41. Not a factual inaccuracy.
British Society for Haematology	84	88	5.2.4	"…targeting of RAADP based on immunological RhD typing of the father is cost-effective compared to the use of NIPT". However, there is always the risk that the partner may not be the father.	Not a factual inaccuracy. No comments.
British Society for Haematology	85	71 116	4.3.1 SA3	"…reduce the false positive rate by further targeted testing of women with an initially inconclusive result" "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" Management of inconclusive results could increase costs.	See response to comment 50.
British Society for Haematology	86	91	6.1.2	Recent BCSH guidance on blood grouping and antibody testing in pregnancy (2016) has recommended that women with anti-D detectable at or before 28 weeks (regardless of previous administration of anti-D Ig prophylaxis) should be followed up as if the anti-D is immune, i.e. with serial anti-D quantification, until the anti-D is no longer detectable. This strategy is in response to	Not a factual inaccuracy. No comments.

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				haemovigilance (SHOT) reports where immune anti-D has been incorrectly assumed to by prophylactic anti-D Ig and no interventions have been made, resulting in cases of HDFN. This guidance, if followed, will add to the cost of antenatal testing in the current model of universal anti-D prophylaxis. However, if NIPT is introduced, the increased cost would be 35-40% lower, as women predicted to be carrying a D negative fetus would not receive anti-D Ig for sensitising events in pregnancy. This would affect the cost model in favour of NIPT.	
British Society for Haematology	87	108 146	6.3.13 7.3.2	The estimated annual costs for minor and major development problems appear an underestimate – if a child has major development problems it's hard to see how this would only cost £574 per year? Also the average cost per sensitisation being estimated to be £3167 seems an underestimate given these pregnancies will need many more clinic appointments, MCA dopplers at regular intervals and potentially in utero transfusions? "…existing evidence informing the impact of sensitisations in terms of their long term health and cost consequences is more limited and highly uncertain" – this is important and if identified could significantly impact the conclusions that would be reached.	See response to comment 48.