NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 17 August 2016

THEME: Inconclusive results and repeat tests

Comment number	Name and organisation	Section number	Comment	Response
1	International Blood Group Reference Laboratory	Page 27, 4.43	We agree that PP3 is the most cost-effective strategy. The rate of "inconclusives" should not affect cost effectiveness if they are true positives. The term "inconclusive" was used during the studies performed in Bristol. We have always advised that all positives and all those where and *RHD* signal was detected in fewer replicates that we termed "inconclusive" during the studies were treated as positive. In retrospect it was unfortunate that we used the term "inconclusive" in the studies as this has made the cost effectiveness analysis more complicated and leads to some confusion. We should consider it as binary: i. Positive (including those reported as inconclusive in the studies) or ii. Negative. We should then only consider iii. false positives where the result is treated as positive, be it reported as positive or inconclusive, but it should have been negative and therefore anti-D was given, and	Thank you for your comment which the committee considered. The committee agreed that reporting the results as either positive or negative would be helpful and less confusing for healthcare professionals interpreting the test and explaining the result to pregnant women. The committee noted that in the model women with inconclusive test results are treated as though the test result was positive. Therefore if postpartum testing continues without any changes to current practice (PP1), changing to reporting inconclusive test results as positive in practice will have no effect on the model's results. The external assessment group noted that there are potential advantages to reporting inconclusive results if there is a change in postpartum testing from testing all women to testing certain subgroups of women. This is because the false positive rate is higher among women with an inconclusive result (around 25% in the Bristol studies) than among women with a conclusive positive test (around 1.3%).

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			iv. False negatives where anti-D was not given, but it should have been.	Postpartum testing to identify false positive NIPT results may lead to reduced use of unnecessary postpartum anti-D immunoglobulin in women whose baby was identified *RHD* positive by NIPT, but confirmed as RhD negative by cord blood typing. If postpartum testing is used in women who had an inconclusive NIPT result, then a greater proportion of false positives would be identified than if the test was used in women who had a conclusive positive NIPT result. Therefore, the cost to benefit ratio of a postpartum testing strategy to identify women with false positive NIPT results (to reduce unnecessary postpartum anti-D immunoglobulin) will be more favourable in women with inconclusive NIPT results, than in women with conclusive positive NIPT results. The committee considered that although the modelled postpartum testing strategies showed promise, there was insufficient evidence to recommend alternative postpartum testing strategies at present and concluded that further research needs to be done to understand the practicalities of implementing alternative postpartum testing strategies (see section 6.2 of the diagnostics guidance).

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2	International Blood Group Reference Laboratory	Page 35, 5.12	i. Regarding the need for repeat tests: ▪ The number of repeat tests requests due to rejected samples at receipt is 3% at present. This is due to sample labelling errors which can be reduced by appropriate training of phlebotomy and midwifery staff. ▪ Inconclusive results should not be repeated and pregnant women should be treated as if they were positive. ▪ The true repeat sample rate owing to NHSBT error is 0.02%, based on 1 sample in approximately 5K, since IBGRL started testing. ▪ The repeat sample rate should not affect the cost as rejected tests are not chargeable and a repeat sample can be taken at the next scheduled antenatal appointment.	Thank you for your comment which the committee considered. The external assessment group noted that the cost effectiveness analysis does not assume any impact of repeat sampling on costs. It noted further that in practice if an additional blood draw is required this would be expected to incur some cost, but the absolute cost attributed to repeat sampling is likely to be very small and is unlikely to impact on the cost effectiveness results.

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3	International Blood Group Reference Laboratory	Page 34, 5.10	Activity based costings were provided for sample volumes between 10 and 100K (which included staff, equipment and consumables). The latter figure would cover the cost of implementation throughout England. The approach taken by NICE of stating the test cost below which it would be cost effective (assuming accuracy at least as good as that published) seems very reasonable in the circumstances. Although the final royalty fee is still subject to negotiation, a scenario in which the holders of the IPR charge a fee that would take the test cost above the NICE threshold is unlikely (and it would probably be unreasonable).	Thank you for your comment which the committee considered. The committee concluded that high-throughput NIPT for fetal *RHD* genotype has the potential to be cost effective, but that the cost savings are volatile with respect to the cost of the test (see section 5.11 of the diagnostics guidance) and the costs associated with implementation (see section 5.12 of the diagnostics guidance). The committee decided that although the cost savings are potentially small, recommending high-throughput NIPT for fetal *RHD* genotype would be an effective way of reducing unnecessary use of anti-D immunoglobulin. This consideration is detailed in section 5.15 of the diagnostics guidance.
4	International Blood Group Reference Laboratory	Page 35, 5.12	iv. The cost of the test itself: IBGRL has supplied previously costing which show that the cost per test could be reduced when the referral volume increases. This should give certain stability in the price of the test itself.	Thank you for your comment which the committee considered.

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5	International Blood Group Reference Laboratory	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? a) Page 27, 4.39.	In PP1 cord blood tests would be performed on all RhD negative women and in PP3 only cord blood tests would be performed on women who had RhD negative babies. It would appear that PP3 would in fact be less expensive than PP1 as PP3 saves 60% of cord blood testing but still reduces the risk of any additional sensitisations occurring as a result of false negative predictions by NIPT and provides the same number of QALYs. Should PP3 therefore dominate PP1?	Thank you for your comment which the committee considered. The external assessment group noted that NIPT PP3 increases postpartum care costs because although fewer cord blood tests are done, there is unnecessary use of fetomaternal haemorrhage tests and anti-D immunoglobulin for those who test positive (which includes those who test inconclusive but carry a RhD negative baby). The committee considerations on the cost-effectiveness of the different post-partum testing strategies are detailed in section 5.8 of the diagnostics guidance document.
6	International Blood Group Reference Laboratory	Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?	Testing all cord bloods of RhD negative women may be less cost effective. The error rate in cord testing may be higher than NIPT in fact. Two samples are sent. A maternal blood for blood group and if needed feto-maternal haemorrhage estimation and also a cord blood sample. Confusion can occur when taking these samples, labelling them near the woman	Thank you for your comment which the committee considered. The committee heard from the external assessment group that because both cord blood testing and NIPT for fetal *RHD* genotype are very accurate, human error may be a major cause of false positive or false negative results. The external assessment group noted that it was not possible to quantify

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		Page 32 and 33, 5.7 and 5.8	and booking them into the laboratory. Testing tends to be performed manually as cord samples can cause problems for automated analysers based on the way they are filled and occasionally contamination with material such as Wharton's jelly. Manual testing is associated with an increased analytical and transcription risk. PP3 may therefore be more cost effective than PP1. PP3 would avoid the same false negative predictions as in PP1 but require less tests albeit with a decision point as to whether the woman / cord needed to be tested at all that would not exist with universal testing. The Netherlands initially implemented NIPT with retained cord typing but found that the cord typing did not provide sufficient benefit when the low rate of false negatives identified by NIPT was balanced against the time and cost of the additional cord testing with the associated sample / test error risks.	human error in analyses because data are not available and cord blood testing was therefore assumed to be a perfect "gold standard". The committee heard from clinical experts that postpartum testing involves taking a cord blood sample quickly after the birth, and that although midwives are used to doing this they also have multiple other tasks to complete at this time. The committee was concerned that if midwives had to get the NIPT result and make a decision on whether to take a cord blood sample in the period immediately after the delivery, then errors could be made, for example, not taking a cord blood sample from a fetus predicted to be D negative. The committee also noted the difficulties of taking a blood sample from the cord and that the consequences of a sampling error may including having to take repeat blood samples from a neonate. It therefore decided that further research on the practicalities of implementing alternative postpartum testing strategies would be valuable. A new section (section 5.9) has been added to the

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				diagnostics guidance to detail the committee considerations on these issues. An additional research recommendation has also been added to the diagnostics guidance document which recommends further research on alternative postpartum testing strategies that do not include cord blood typing of all babies born to RhD negative women (section 6.2).

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7	NHS Professional 1	General	This careful and considered review has in my view come to the right conclusion. Offering this test will improve patient care by avoiding unnecessary exposure of young women to anti-D (a multi-donor blood product) in a cost-effective way. As someone who led a pilot implementation (in Bristol / Avon), I know this is not difficult to integrate into current maternity care and by avoiding unnecessary medical interventions in pregnancy, is popular with midwives and pregnant women. We should remain respectful of the difficulty of making anti-D, the sacrifice of the donors and the shortages of anti-D that have occurred at times, so it seems wrong to waste this product in pregnant women who cannot benefit from it. I hope this approach will be rapidly offered nation-wide.	Thank you for your comment which the committee considered.
8	International Blood Group Reference Laboratory	Page 34, 5.10	In England sample transport from maternity clinics and rural areas have established logistic links for transfer of samples to NHS hospitals with Transfusion Laboratories to test their antenatal samples as well as other pathology tests. These NHS hospitals are by necessity linked to the NHSBT transport network as they need to have blood and blood components delivered to them on a frequent basis. This transport mechanism is also already routinely used	Thank you for your comment which the committee considered. The committee was concerned that although there may be no cost for sample transport between the NHSBT units and the IBGRL, there may be a cost for transporting the sample from the maternity clinic to the NHSBT unit. This consideration is detailed in section 5.11 of the

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			by hospital pathology services to transport samples to NHSBT's reference laboratories and return empty blood component delivery containers. All hospital transfusion laboratories utilise this service and for this reason there will be no additional cost for NIPT samples. In addition all hospitals in England have access to NHSBT's online reporting system using Sunquest's Integrated Clinical Environment (Sp-ICE) and can access reports without necessarily needing a paper copy.	diagnostics guidance. The committee recommended that data on the cost of sample transport is collected and analysed as part of further research; detailed in section 6.1 of the guidance document.
9	International Blood Group Reference Laboratory	Page 35, 5.12	i. See comment regarding transport under response 8 above (referring to page 34 section 5.10 from the draft document)	Thank you for your comment which the committee considered. The committee was concerned that although there may be no cost for sample transport between the NHSBT units and the IBGRL, there may be a cost for transporting the sample from the maternity clinic to the NHSBT unit. This consideration is detailed in section 5.11 of the diagnostics guidance. The committee recommended that data on the cost of sample transport is collected and analysed as part of

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				further research; detailed in section 6.1 of the guidance document.
10	International Blood Group Reference Laboratory	Page 35, 5.12	iii. Midwife time should not increase due to counselling and seen as been offset by a reduction of 40% during the 28 week RAADP clinic. Please note that NHSBT provides a Patient Information Leaflet on high throughput NIPT for fetal RHD genotyping to support pregnant women and midwifes aiding consent (link to leaflet http://hospital.blood.co.uk/media/27899/inf1263-11-mothers-blood-test-to-check-her-unborn-babys-blood-group.pdf)	Thank you for your comment which the committee considered. The committee noted that a patient information leaflet explaining the test and its results was available from NHSBT. This information has been added into section 5.12 of the diagnostics guidance.
11	International Blood Group Reference Laboratory	Page 35, 5.12	v. See also the comment regarding online results through Sp-ICE in point 8 above.	Thank you for your comment which the committee considered. The committee noted that not all midwives have access to the Sp-ICE system, therefore a paper copy of the test results is often needed. Further, it heard from clinical experts that in some instances data from Sp-ICE are not shared between trusts and paper copies of results are required for womens' maternity records so information is available if they present to a maternity unit other than the

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				one they are booked at.
12	NHS Professional 2	General	We introduced ffDNA testing on 1.6.16, and will be following the pathway described on page 38 as '5th pathway' with cord testing on fetuses predicted to be Rhesus negative or with inconclusive results. We have had excellent acceptance amongst Rhesus negative women so far. We have not encountered any training challenges amongst clinical or laboratory staff. We have had excellent IT input, with the fetal result arriving electronically into our reporting system in a timely fashion. We are doing a prospective evaluation as we go along, to ensure that the predicted cost neutrality is achieved - our planning suggests that we will make a small cost saving, but our main drive has been to improve the patient pathway.	Thank you for your comment which the committee considered.

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THEME: General

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13	International Blood Group Reference Laboratory	Has all of the relevant evidence been taken into account?	In our opinion all the evidence we are aware of has been considered	Thank you for your comment which the committee considered.
14	Royal College of Nursing	General	The Royal College of Nursing have no comments to submit to inform on the DCD at this time.	Thank you for your comment which the committee considered.