NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of DG25: High-throughput non-invasive prenatal testing for fetal RHD genotype

This guidance was issued in November 2016.

The review date for this guidance is November 2019.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Review decision

Transfer the guidance to the 'static guidance list'. To remove the research recommendation and highlight that relevant research has been undertaken.

That we should not consult on the proposal.

A list of the options for consideration, and the consequence of each option is provided in Appendix 1 at the end of this paper.

2. Rationale

Since the publication of DG25, there have been no changes to the technology. New evidence has become available on the use of NIPT, however, none of these studies are likely to lead to a material change to the original recommendations. Therefore, the guidance should be transferred to the static list.

3. Original objective of guidance

To assess the clinical and cost effectiveness of high-throughput non-invasive prenatal testing for fetal RHD genotype.

4. Current guidance

Adoption recommendations

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

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

Research recommendations

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

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

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

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

5. Implications for other guidance producing programmes

No overlaps were identified.

6. New evidence

The search strategy from the original diagnostics assessment report was re-run on MEDLINE, CINAHL, Cochrane Database of Systematic Reviews (CDSR), EMBASE, CRD Health Technology Assessment database, and the Science Citation Index. References from January 2016 to March 2020 were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Companies were asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. Specialist committee members for this guidance topic were also consulted and asked to submit any information regarding changes to the technology, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below.

6.1 Technologies

Since the publication of NICE's diagnostics guidance 25 in November 2016, there have been no technical changes to high-throughput NIPT for fetal RHD genotype. The technology remains available and is still being used in the NHS. The International Blood Group Reference Laboratory (IBGRL) moved from a Clinical Pathology Accreditation (CPA) to a United Kingdom Accreditation Service (UKAS) accreditation shortly after DG25 was published. Consequently, the fetal RHD screening test is UKAS accredited to ISO15189. No new technologies performing a similar function to the high-throughput NIPT for fetal RHD genotype were identified.

The unit cost per sample depends on the total uptake of NIPT, it takes into account consumables, staffing, equipment, indirect and overhead costs. Compared to the

original submission the test is now [redacted] cheaper per sample.

6.2 Clinical practice

One specialist committee member noted that since publication of DG25 the care pathway had changed in their trust. High-throughput NIPT is now offered in this trust at approximately the 16th week appointment and the test results influence the postnatal pathway. Similarly, in a study carried out by the Cedar External Assessment Centre (EAC) to address the research recommendations in DG25, it was found that the test was implemented through existing routine appointments and that no extra appointments were required. IBGRL did not note any changes in the care pathway.

In DG25 four alternative ways in which high-throughput NIPT could affect the existing postpartum care pathway were considered:

- Postpartum scenario 1 (PP1): postpartum cord blood typing and fetomaternal haemorrhage testing would continue to be done, based on current guidelines, in all women regardless of the fetal *RHD* genotype identified with high-throughput NIPT.
- Postpartum scenario 2 (PP2): postpartum cord blood typing and fetomaternal haemorrhage testing (and by implication anti-D immunoglobulin) would be withheld if high-throughput NIPT for fetal *RHD* genotype identified a D-negative fetus, but would continue to be done if high-throughput NIPT was inconclusive or had identified a D-positive fetus.
- Postpartum scenario 3 (PP3): postpartum cord blood typing would be done if high-throughput NIPT for fetal *RHD* genotype identified a D-negative fetus. Fetomaternal haemorrhage testing and post-delivery anti-D immunoglobulin would be provided if high-throughput NIPT was inconclusive or identified a D-positive fetus.
- Postpartum scenario 4 (PP4): postpartum cord blood typing would not be carried out in any women. Fetomaternal haemorrhage testing and post-delivery anti-D immunoglobulin would be provided if high-throughput NIPT was inconclusive or had identified a D-positive fetus.

DG25 considered a fifth postpartum strategy (PP5) in which, postpartum cord blood testing is done if high-throughput NIPT for RHD test identifies RHD negative fetus or results are inconclusive. The Kleihauer test (along with postpartum anti-D

prophylaxis) is done if the RHD positive fetus is identified by either the NIPT for RHD test or cord blood testing of inconclusive test result.

Since the publication of DG25, NICE's guideline on Abortion care (2019) recommends anti-D prophylaxis for women who are rhesus D negative and are having an abortion after 10^{+0} weeks' gestation. Advice to providers includes ensuring availability of rhesus status testing and anti-D prophylaxis supply to avoid delays to women having an abortion. NICE's guidance on Antenatal care for uncomplicated pregnancies was updated to link the relevant recommendation on anti-D prophylaxis to DG25. Following the publication of DG25, there have been no material changes to the recommendations made regarding anti-D prophylaxis in NICE's Technology appraisal guidance on Routine antenatal anti-D prophylaxis for women who are rhesus D negative and the NICE guideline on Ectopic pregnancy and miscarriage: diagnosis and initial management.

6.3 New studies

Four clinical and 2 economic studies were identified through the literature search; none of the studies were carried out in the UK (Norway, USA, Canada, Finland, Netherlands or Australia). All clinical studies assessed the diagnostic accuracy of the NIPT fetal RHD genotyping. Compliance to the new testing strategy was reported in 2 studies.

Clinical case series

De Haas (2016) was a diagnostic accuracy study comparing non-invasive fetal RHD testing (between 27th and 29th week gestation) with cord blood typing for 25,789 women (32,222 samples) in the Netherlands. The data was collected between 4th of July 2011 to 7th of October 2012. Outcomes on diagnostic accuracy and compliance (test requested and performed) were reported. De Haas (2016) follows up from the publication by De Haas et al. (2012), included in Diagnostic Assessment Report for DG25, but presents longer time period of data collection and includes more patients. The mean gestational age was 27 weeks+6days (SD 0+6). The fetal RHD results were: 19,862 positives (61.6%), 12,360 negatives (38.4%). The false negative rate was 0.03% (95%CI 0.02% to 0.07%) and the false positive rate was 0.57% (95%CI 0.49% to 0.68%). Test sensitivity and specificity were 99.94% (95%CI 99.89% to 99.97%) and 97.74% (95%CI 97.43% to 98.02%), respectively. Compliance rate was 96.3% for the first year after implementation.

Haimila (2017) was a diagnostic accuracy study which compared results of non-invasive fetal RHD testing to cord blood typing or heel stick test for 10,814 women in Finland between February 2014 and January 2016. Patients were tested between

the 24th and 26th week of gestation. The mean gestational age was not reported. The non-invasive fetal RHD results were: 7,087 positive (65.5%), 3,641 negative (33.7%) and 86 inconclusive (0.8%). There were 7 false positives and 1 false negative result. Test sensitivity and specificity were 99.99% (95%CI 99.92% to 99.99%) and 99.81% (95%CI 99.6% to 99.92%), respectively. Test accuracy was 99.93% (95%CI 99.85 to 99.97%). Compliance was 69.7% for the first year after implementation, 97.3% during the second year and rose to 98.3% by the end of the study period (the last 6 months).

Moise (2016) was a diagnostic accuracy study presenting data for 520 non-RHD immunised RhD negative women who were tested using NIPT in each trimester (467 tests in the 1st trimester, 458 in the 2nd and 425 in the 3rd) in the USA and Canada between September 2009 and April 2011. The comparator was cord blood typing. The mean gestation age at testing was 12.3 weeks (range 10.7-14.7) in the 1st trimester, 18 weeks (range 15.1-24.4) in the 2nd and 28.7 weeks (range 26-32.4) in the 3rd. The test results in the 1st trimester were: 312 positive (66.8%), 129 negative (27.6%) and 26 inconclusive (5.7%); 2nd trimester: 303 positive (66.2%), 129 negative (26.4%) and 26 inconclusive (5.7%); 3rd trimester: 278 positive (65.4%), 121 negative (28.5%) and 26 inconclusive (6.1%). There were 2 false positives in the 1st trimester, 2 in the 2nd trimester and 1 in the 3rd trimester. Only 1 false negative result (in the 1st trimester due to mislabelling) was recorded. Test sensitivity was: 99.68% (95%CI 98.22–99.94%) in the 1st, 100% (95%CI 98.74–100%) in the 2nd and 100% (95%CI 98.63–100%) in the 3rd trimester. Test specificity was 98.46% (95%CI 94.56–99.58%) in the 1st, 98.47% (95%CI 94.60–99.58%) in the 2nd and 99.18% (95%CI 95.50–99.96%) in the 3rd trimester. Test accuracy was 99.32% (95%CI 98.03–99.77%) in the 1st, 99.53% (95%CI 98.33–99.87%) in the 2nd and 99.75% (95%CI 98.59–99.99%) in the 3rd trimester.

Sorensen (2018) was a diagnostic accuracy study presenting data for 373 samples from RHD negative pregnant women in Norway between 2011 and 2013. Median gestational age was 24 weeks (range 16-36). The results of non-invasive fetal RHD testing were compared with cord blood typing. The fetal RHD results were: 234 positive (62.7%), 127 negative (34%) and 12 inconclusive (32.2%). There was 1 false positive and no false negative results. Test sensitivity and specificity were 100% (95%CI 98.4-100%) and 99.2% (95%CI 95.7-100%), respectively.

Economic evaluation (cost-effectiveness analysis)

Gordon (2017) assessed the cost-effectiveness of non-invasive fetal RHD genotyping and targeted anti-D prophylaxis versus current practice in Australia. The model was a decision tree with 2 scenarios: current practice (no non-invasive fetal RHD genotyping with universal anti-D prophylaxis) and non-invasive fetal RHD

genotyping with targeted anti-D prophylaxis. The mean cost per person for the non-invasive RHD genotyping was calculated as AU$45.48 (US$31.84). Mean overall cost per pregnancy was AU$7495 (US$5247) for standard care and AU$7471 (US$5230) for non-invasive RHD genotyping. Under non-invasive RHD genotyping, if all babies received cord blood serology, the mean cost was AU$7480 (US$5236) and excluding it was AU$7465 (US$5226) per pregnancy. Non-invasive RHD genotyping had a 96.8% probability of being cost-effective at a willingness to pay of AU$50,000 per healthy baby.

Moise (2019) assessed the cost-effectiveness of 3 different strategies for antenatal anti-D administration in a US population. The model was a decision tree with 3 scenarios: application of anti-D prophylaxis in all non-immunized RhD-negative women with or without a paternal RhD-positive serologic result (scenario 1 and 2, respectively) and non-invasive RHD genotyping of all non-immunized RhD-negative women before 28 weeks of gestation, with anti-D prophylaxis given when fetus tests RhD-positive. Charges in first pregnancy (best / worst case scenario) were $663.8/$663.8 for scenario 1, $722.3/$722.3 for scenario 2 and $869.3/$874.59 for scenario 3. Charges in the second pregnancy (first alloimmunized pregnancy; best / worst case scenario) were $4.78/$9.44 for scenario 1, $3.55/$7.01 for scenario 2, $3.76/$8.07 for scenario 3. Over both pregnancies, the charges favour scenario 1, followed by scenario 2 and then 3.

6.4 NICE's research commissioning activities

In the original guidance, recommendations were made for further research into the costs and resource use associated with implementing the high-throughput NIPT for fetal RHD genotyping and for alternative postpartum strategies that do not involve cord blood typing of all babies born to RhD negative women.

Cedar EAC was commissioned to address the research recommendations in DG25. Ryczek et al (2020) investigated the implementation, uptake and adherence to routine anti D prophylaxis through a survey sent to 39 hospital trusts in England and semi-structured telephone interviews with 7 healthcare professionals. Additional data was gathered from IBGRL and an update of the literature review for DG25.

The report explored the issue of training on the procedure and how to access NIPT for foetal RHD genotype reports and recording results appropriately. Based on responses received the largest group of healthcare professional who require the training are midwives. Doctors and laboratory staff may require training. The training typically lasts about 30 minutes.

An assessment of audit data and cost analysis of some routine resources used in implementing the service (including, sample management, record keeping, informing patient) showed that the service is cost neutral or saving. None of the responding trusts had need for additional arrangements for sample collection, however, on some occasions such as long weekends, special delivery arrangements may be made. Sixty-three percent of respondents incurred no extra costs with sample management. Test repeats, additional sample bottles and charges for mislabelled samples could result in additional costs. Most respondents (65%) noted that record keeping took extra time. A lack of uniformity between IT systems used by trusts and NHSBT could results in transcription errors.

Respondents noted that no extra appointments were required to explain the test, take consent, present results or provide information on management. Cost savings were stated to be achieved due to a reduction in anti-D use, sample testing (cord blood typing and Kleihauer test) and the resources needed to quantify the dose of anti-D required.

The survey suggests uptake of the new service is high; however, the data on uptake of NIPT is not routinely monitored. The frequency of positive, negative and inconclusive results is 55.9%, 34,5% and 4.3% respectively. Data on the adherence to routine antenatal anti-D Prophylaxis (RAADP) is not routinely monitored in most trusts. Sixty-nine percent of respondents noticed no changes in uptake of or compliance with RAADP since the service was implemented.

Nineteen survey responses were received on the use of alternative postpartum testing strategies following the NIPT for fetal RHD genotype (cord blood testing and the Kleihauer test). Six trusts use the PP5, 5 trusts use the PP1 and 4 trusts use the PP3 strategies noted on page 5. Four trusts used a modified PP5 strategy in which cord blood testing is done for all babies regardless of their NIPT result and the Kleihauer test is done only for predicted or confirmed RhD-positive babies.

7. Summary of new evidence and implications for review

The new clinical evidence identified for this review include four diagnostic accuracy studies, none of which were carried out in the UK. The generalisability of the new evidence to current clinical practice in the UK may be limited given the variation in the timing of the test. The timing of the of the test has an impact on the number of false negative rates and inconclusive results. As noted in DG25, the number or false-negatives and the percentage of inconclusive results are higher before the 11th week of gestation. In addition, one of the studies used cord blood typing along with heel stick test as a reference standard to confirm RhD status of newborns.

In the included studies, positive and negative test results ranged from 61.6% to 66.8% and 26.4% to 38.4% respectively, while inconclusive results were observed in 0.8% to 6.1% of patients. These rates are comparable to the findings in DG25. Information supplied from IBGRL to Cedar as part of the audit, showed that between April 2017 and October 2018 in hospitals in England, the average percentage of positive results was 55.9%, negative 34.5% and inconclusive 4.3%. Approximately 5.4% of the samples were not tested, for example due to mislabelling errors. Sensitivity and specificity in the new studies were greater than 99% and 97% respectively and these are comparable to the findings in DG25. The rates of compliance reported in 2 studies were 96.3% and 69.7% for the first year after implementation and these are also consistent with the findings in DG25.

The 2 economic studies identified were done outside the UK and report conflicting results about the cost of implementing a NIPT for fetal RHD genotyping service.

Since the publication of DG25, there have been no changes to the technology. New evidence has become available on the use of NIPT, however, none of these studies are likely to lead to a material change to the original recommendations. In line with the original recommendations on cost savings audit data and cost analysis showed that implementation and delivery of the service are cost neutral or cost saving. The implementation of the test is done at existing appointments in the pathway. NICE is proposing a transfer of the guidance to the static list.

8. Implementation

At the time of publishing the original guidance approximately [redacted] samples were received per month from only [redacted] Trusts. The test is currently under contract with [redacted] NHS Trusts with samples received from [redacted] Trusts. The number of samples received per month was [redacted] – [redacted] at the end of 2019.

9. Equality issues

In the original guidance it was noted that having anti-D immunoglobulin may not be acceptable by some women for personal, cultural and religious reasons. Also highlighted was the point that D-negative women of black African family origin are more likely to have an RHD pseudogene, and so are more likely to have an inconclusive or false-positive NIPT result compared with women from other ethnic family origins.

GE paper sign off: Rebecca Albrow, Associate Director, March 2021

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Appendix 1 – explanation of options

If the published Diagnostics Guidance needs updating NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
Standard update of the guidance	A standard update of the Diagnostics Guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the Diagnostics Guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Diagnostics Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Diagnostics Guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No

Withdraw the guidance	The Diagnostics Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

Antenatal and postnatal mental health: clinical management and service guidance (2014, updated 2020) NICE guideline CG192

Abortion care (2019) NICE guideline NG140

Antenatal care for uncomplicated pregnancies (2008, updated 2019) NICE guideline CG62

Ectopic pregnancy and miscarriage: diagnosis and initial management (2019) NICE guideline NG126

Fertility problems: assessment and treatment (2013, updated 2017) NICE guideline CG156

Jaundice in newborn babies under 28 days (2010, updated 2016) NICE guideline CG98

Postnatal care up to 8 weeks after birth (2006, updated 2015) NICE guideline CG37

Safe midwifery staffing for maternity settings (2015) NICE guideline NG4)

In progress

Postnatal care NICE clinical guideline. Publication expected November 2020

Antenatal care NICE clinical guideline. Publication expected April 2021

Babies, children and young people's experience of healthcare NICE clinical guideline. Publication expected April 2021

Details of new technologies

None

Registered and unpublished trials

None

References

De Haas M., et al. (2012) A nation-wide fetal RHD screening programme for targeted antenatal and postnatal anti-D. ISBT Science Series 7: 164-7.

De Haas M., (2016) Sensitivity of fetal RHD screening for safe guidance of targeted anti-D immunoglobulin prophylaxis: prospective cohort study of a nationwide programme in the Netherlands. BMJ 355:i5789.

Gordon L.G., et al. (2017) Noninvasive fetal RHD genotyping of RhD negative pregnant women for targeted anti-D therapy in Australia: A cost-effectiveness analysis. Prenatal Diagnosis 37: 1245-1253.

Haimila K., et al. (2017) Targeted antenatal anti-D prophylaxis program for RhD-negative pregnant women – outcome of the first two years of a national program in Finland. Acta Obstetricia et Gynecologica Scandinavica 96: 1228-1233.

Moise K.J., et al. (2016) Circulating Cell-Free DNA to Determine the Fetal RHD Status in All Three Trimesters of Pregnancy. Obstetrics & Gynecology 128(6): 1340-1346.

Moise K.J., et al. (2019) Cell free fetal DNA to triage antenatal rhesus immune globulin: Is it really cost-effective in the United States? Prenatal Diagnosis 39: 238-247.

NICE Diagnostic assessment report (2016) 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. Available at https://www.nice.org.uk/guidance/dg25/documents/diagnostics-assessment-report (last Accessed April 2020)

Sorensen K., et al. (2018) Determination of fetal RHD type in plasma of RhD negative pregnant women. Scandinavian Journal of Clinical and Laboratory Investigation 78(5): 411-416

Ryczek E., White J., Carolan-Rees G. (2019) Evaluation of implementation of high-throughput Non-Invasive Prenatal Testing (NIPT) for foetal RHD genotype testing: results of a survey of maternity units in England, supplemented by expert elicitation findings Implementation Science 14(Suppl 2):O17