



Adoption support resource – insights from the NHS

Implementation support

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1 Introduction

This resource has been developed to provide practical information and advice on NICE diagnostics guidance on [high-throughput non-invasive prenatal testing for fetal RHD genotype](#).

The information presented in this resource is intended for the sole purpose of supporting the NHS in adopting, evaluating the impact of adopting or further researching this technology. It is complementary to the guidance and was not considered by the diagnostic assessment committee when developing its recommendations.

The technology for high-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* genotype is a laboratory-developed test, offered by [NHS Blood and Transplant \(NHSBT\)](#), Bristol. Regional variations in terminology include cell-free fetal DNA (cffDNA), free fetal DNA (ffDNA) and fetal rhesus status testing. Some of these terms are used in this report in the context of local examples.

The technology uses a real-time quantitative polymerase chain reaction (PCR) method for identifying fetal *RHD* genotype from fetal DNA in the plasma of rhesus-D (D) negative women. It can rapidly process batches of between 32 and 88 samples (see section 3 of the [guidance](#)).

The benefits of using high-throughput NIPT for fetal *RHD* genotype to guide antenatal prophylactic treatment with anti-D immunoglobulin as reported by the NHS staff involved in producing this resource include:

- preventing unnecessary administration of blood products (anti-D immunoglobulin) and their associated risk
- avoiding unnecessary painful injections for women when the NIPT for fetal *RHD* genotype result is negative
- reducing the number of antenatal anti-D prophylactic clinic appointments needed, and the amount of anti-D immunoglobulin used
- increasing the availability of anti-D immunoglobulin for use after potentially sensitising events in pregnancy when the NIPT result for fetal *RHD* genotype is positive

- reducing the anxiety associated with potentially sensitising events for D-negative women when the NIPT result for fetal *RHD* genotype is negative
- providing information to allow D-negative women to make an informed decision about whether to have treatment with anti-D immunoglobulin.

NHS contributors also reported that services should be aware of the possibility of false-negative test results when deciding to introduce the test.

2 Current practice

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

If sensitisation happens, the immune response is quicker and much greater when the mother is exposed during a later pregnancy to D antigen from a D-positive fetus. The anti-D produced by the mother can cross the placenta and cause haemolytic disease of the fetus and newborn. This can cause severe fetal anaemia, leading to fetal heart failure, fluid retention and swelling (hydrops), and intrauterine death.

Routine antenatal anti-D prophylaxis (RAADP) for all women who are D-negative is the current practice in most NHS maternity services. Confirming the blood group of a baby born to a D-negative mother by taking a cord blood sample is routine postpartum clinical practice.

The NICE technology appraisal guidance on [routine antenatal anti-D prophylaxis for women who are rhesus D negative](#) recommends that all pregnant women who are D-negative are offered prophylactic anti-D immunoglobulin in the third trimester. This is generally offered at the 28-week antenatal appointment, but a 2-dose regime may be offered at 28 and 34 weeks. The NICE technology appraisal guidance and NICE diagnostic guidance should be read together.

The British Committee for Standards in Haematology's guideline on the [use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn](#) also recommends that all D-negative pregnant women who are not known to be sensitised to D antigen have anti-D immunoglobulin after:

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

The NICE diagnostics guidance states that about 40% of D-negative women carry a D-negative fetus and do not need anti-D immunoglobulin if the rhesus-D status of the

fetus can be determined. A small number of organisations have already implemented high-throughput NIPT for fetal *RHD* genotype into routine practice to target this group of women and prevent unnecessary prophylactic treatment.

3 Summary of NICE recommendations

The NICE [diagnostics guidance](#) and this adoption support resource specifically relate to high-throughput non-invasive prenatal testing for fetal *RHD* genotype.

High-throughput 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.

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. High-throughput refers to automated instead of manual testing.

NICE also recommended further [research](#) on:

- Data collection and analysis of the costs and resource use associated with implementing high-throughput non-invasive prenatal testing for fetal *RHD* genotype to show the overall cost of testing and to inform any future update of the guidance.
- Alternative postpartum testing strategies that do not include cord blood typing of all babies born to rhesus D (D) negative women.

4 Tips for adopting high-throughput NIPT for fetal *RHD* genotype

The NHS contributors to this resource considered the following to be important:

- Consider whether a pilot period is appropriate.
- If the pregnant women in the population are known to move across geographical health boundaries, the potential benefits of joint implementation with neighbouring organisations should be assessed.
- Establish who is responsible for ordering, stocking, issuing, funding and the contractual arrangements for anti-D immunoglobulin. Review the annual contract for anti-D procurement to avoid over ordering and waste (see [assessment of readiness](#)).
- Assess the interoperability of the:
 - local system for requesting tests and reporting results
 - local laboratory information management system
 - [specialist services electronic reporting system](#) (Sp-ICE) system used by the NHSBT (see [assessment of readiness](#)).
- Complete a resource impact assessment to see if local implementation will be cost effective as outlined in the NICE guidance (see [resource impact](#)).
- Identify how the service will be measured in terms of quality and safety, patient experience, productivity and improved clinical outcomes. Consider what baseline assessment will be used and how to monitor uptake of the test (see [measuring success](#)).
- Develop and prioritise a staged training plan for the various staff groups (see [education and communication plans](#)).
- Develop a staged communication plan to raise awareness among staff and patients before implementation and again before the time of delivery (see [education and communication plans](#)).

- Include a flowchart in the protocols and local guidelines (see [develop local documentation](#)).

5 How to implement NICE's guidance on high-throughput NIPT for fetal *RHD* genotype

NHS contributors to this resource have worked with NICE to develop practical suggestions on how to implement NICE guidance on high-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* genotype. Table 1 gives a summary of the contributing sites' demographics. The individual site case studies are presented on the NICE shared learning database.

Table 1 Contributor demographics

Site	Implementation lead	Midwifery service structure	Babies delivered annually (n)	Date technology implemented	Gestational stage for taking NIPT RHD sample	NHSBT cffDNA costing spreadsheet ¹
West Middlesex University Hospital, Chelsea and Westminster Hospital NHS Foundation Trust	Consultant obstetrician and gynaecologist	Core labour ward midwives and core community midwives	5,000 to 5,500	June 2016	16 weeks	Cost neutral
Harrogate and District NHS Foundation Trust	Transfusion practitioner	Integrated between community and delivery suite	1,800	May 2016	16 weeks	Slight cost saving

Taunton and Somerset NHS Foundation Trust	Laboratory manager ² , consultant haematologist and midwifery matron	Integrated community and birth centre midwives	3,300	February 2016	16 weeks	Marginally cost incurring
University Hospitals Bristol NHS Foundation Trust	Midwifery matron	Separate hospital and community-based staff	5,500	April 2013 (pilot) Routine practice 2014	16 weeks	Cost neutral
Yeovil District Hospital NHS Foundation Trust	Laboratory manager ² , antenatal and newborn screening co-ordinator, antenatal clinic lead and bereavement midwife	Integrated community and labour ward midwives	1,500	February 2016	12 weeks	Cost neutral

Abbreviations: cffDNA, cell-free fetal DNA; NHSBT, NHS Blood and Transplant; NIPT non-invasive prenatal testing.

¹ The NHSBT cffDNA costing spreadsheet was used by the contributors before the NICE diagnostic guidance and relevant resource impact template were developed.

² The laboratory manager is employed by Integrated Pathology Partnerships (iPP), part of a joint venture (Southwest Pathology Services LPP) with Taunton and Somerset and Yeovil District Hospital NHS Foundation Trusts and Integrated Pathology Partnerships. Pathology Services for both NHS foundation trust joint venture partners are provided by iPP.

The experiences of NHS organisations have been used to develop practical suggestions on how to implement NICE guidance on high-throughput NIPT for fetal *RHD* genotype. Local organisations will need to assess the applicability of the learning from the examples of current practice, taking into consideration the time, resources and costs of an implementation programme. To implement this technology into routine practice, contributors to the resource suggest taking the following steps.

Project management

This technology can be best adopted using a project management approach. NICE has produced the [into practice guide](#), which includes a section on what organisations need to have in place to support the implementation of NICE guidance.

Implementation team

The first step is to form a local implementation team who will work together to implement the technology and manage any changes in practice.

Individual NHS organisations will determine the membership of this team and how long the project will last. In order to implement this guidance in an effective and sustainable way, consider the following membership of the team:

- Clinical champion(s): this could be a senior clinician or manager with an interest in maternity care, transfusion services or antenatal screening. They should have the relevant knowledge and understanding to answer any clinical queries and promote the project at a senior level.
- Project manager: this could be someone in a clinical or managerial role who will be responsible for the day-to-day running of the project, co-ordinating the project team and ensuring the project is running as planned.
- Management sponsor: they will be able to help assess the financial viability of the project, formulate a business case and help to demonstrate the cost savings achieved.
- Haematologist: they will lead on development of a protocol on how to manage false-negative and false-positive test results.
- Laboratory manager: they will help to develop the process for sending samples and receiving and reporting results.
- IT manager: they will help to identify interoperability of the NHSBT reporting system Sp-ICE and the local diagnostic request and reporting system.
- Midwifery team leaders from community and hospital and advanced practitioners, if appropriate. They will help to develop local processes and to make sure the proposed project is feasible.

- Pharmacy or transfusion practitioner lead: they will help to provide information and costs for anti-D immunoglobulin stock management.
- Consultant obstetrician and other clinicians who may wish to be involved and understand the effect on their services.
- Clinical audit facilitator: they will help to set up mechanisms to collect and analyse local data related to the project metrics and audit needs.
- Clinicians and commissioners from neighbouring health organisations, if there is a local service agreement for providing care across a health boundary or if a joint implementation is planned.

Assessment of readiness

Questions the project team may wish to consider when preparing to adopt this technology are:

- Will it be implemented as an option or a change in the care pathway for all?
- Will there be a change to the postpartum care pathway (see [care pathway mapping](#))?
- What diagnostic request and reporting system is in place and are there any interoperability issues?
- Are there IT access and connectivity issues that mean that the test will need to be asked for on paper?
- How will results be reported?
- Who will be the point of contact in the organisation for clinicians and NHSBT if there are any sampling issues?
- Would it be beneficial to implement the guidance with other local healthcare organisations and commissioners?
- Will a pilot period be helpful?
- The trust may wish to assess local readiness by using a self-assessment tool, which can be amended locally.

Resource impact

NICE estimates that around 95,000 women who are rhesus-D (D) negative and pregnant, and are not known to be sensitised to the rhesus-D antigen, may be eligible for testing with high-throughput NIPT in England.

The number of women estimated to have high-throughput NIPT each year is 90,200 from year 3. The annual saving associated with implementing the guidance is around £371,000 for England. This is equivalent to around £689 per 100,000 population.

It is recommended that adopting organisations complete a resource impact assessment to identify if the technology will be cost neutral, cost saving or cost incurring. NICE has published a [resource impact report](#) and [resource impact template](#) that can be used by NHS commissioners and providers to better understand the local costs associated with adopting high-throughput NIPT for fetal RHD genotype. The national assumptions used in the NICE resource impact template can be altered to reflect local circumstances and the following variables need to be understood to do this:

- births per year
- existing process for routine antenatal anti-D prophylaxis (RAADP) dose (1- or 2-dose regime)
- costs:
 - anti-D immunoglobulin
 - high-throughput NIPT for fetal RHD genotype
- expected referral volume for high-throughput NIPT for fetal RHD genotype:
 - number of tests predicted to be positive (estimated 60% of woman will have anti-D immunoglobulin)
 - number of tests predicted to be negative (estimated 40% of woman will not have anti-D immunoglobulin)
- potentially sensitisation event rates (calculated according to the previous number of potentially sensitising events recorded)
- existing process for managing potentially sensitising events

- cost of test for fetomaternal haemorrhage (FMH) estimation.

Before to the development of the NICE resource impact template, all contributors to this resource found it beneficial to use the cell-free fetal DNA (cffDNA) costing spreadsheet provided by NHSBT, with 3 reporting it to be cost neutral, 1 stating it was marginally cost incurring and 1 reporting slight cost saving.

It is important to clarify the postpartum pathway before using the NHSBT cffDNA costing spreadsheet because it does not account for cord blood grouping at birth for all babies. If all babies will have cord blood grouping at birth, the assumption needs to be altered to reflect this, which may reduce savings. Assumptions in the NHSBT cffDNA costing spreadsheet can be altered to reflect anti-D immunoglobulin, FMH and cord blood group costs and D-negative and D-positive rates. This information could be obtained from pharmacy, transfusion department and laboratory colleagues.

Potential users are advised to contact NHSBT for further advice and support on using the NHSBT cffDNA costing spreadsheet.

Business case

Producing a business case should be a priority for the implementation team. Local arrangements for developing and approving business plans will vary from trust to trust, and each organisation is likely to have its own process in place.

The business case for high-throughput NIPT for fetal *RHD* genotype should include:

- NICE and other national guidance
 - NICE diagnostics guidance on [high-throughput non-invasive prenatal testing for fetal RHD genotype](#)
 - NICE guideline on [antenatal care for uncomplicated pregnancies](#)
 - NICE technology appraisal guidance on [routine antenatal anti-D prophylaxis for women who are rhesus D negative](#)
 - British Committee for Standards in Haematology (BCSH) guideline on [blood grouping and antibody testing in pregnancy](#)
 - BCSH guideline for the [use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn](#)
 - Royal College of Obstetricians and Gynaecologists' guidance on [the management of women with red cell antibodies during pregnancy](#)
- resource impact assessment
- reference to the ethical and physiological benefits of targeting RAADP
- literature on NIPT for fetal *RHD* genotype from NHSBT.

Care pathway mapping

Individual organisations need to consider at what point to implement the guidance, and what changes to the current pathway may be needed.

Consideration needs to be given to:

When and how to gain patient consent – this could be a change in practice; women who have previously had RAADP may need additional support and information to make an informed decision to consent. Sites advised that their first communication with women was either by telephone or letter after they are identified as D-negative (when done at the 16-week appointment), or face-to-face at the 12-week appointment.

Point in the pathway for taking sample – the location, stage of gestation and local uptake of maternity appointments may help to decide at what point in the pathway the test should be offered to optimise uptake. Four of the 5 sites implemented the technology at the

16-week community midwife appointment. The fifth site incorporated it into the hospital-based first trimester screening appointment with an advanced practitioner. The technology is valid after 11 weeks and all sites reported that a cut-off of 26 weeks was used. If 12 weeks is chosen and the woman's blood group is not known, or there is uncertainty about the accuracy of her gestational stage, the community team will need to be informed and asked to test at 16 weeks.

Appointment time – identify if additional time is needed for counselling. Sites allocated appointments of 15 to 20 minutes, and none reported that an increase in appointment time had been needed to provide support for consent or to take the sample.

Accountability – establish who will do the test and who is responsible for acting on the result. Four sites reported that the clinician who asked for the test has responsibility for checking and acting on the result. At the fifth site, the advanced practitioner takes the sample and the community midwives are responsible for checking the result.

Postpartum pathway – the implementation team will need to decide if there will be a change to postpartum cord blood testing. Four of the contributing sites have not changed postpartum pathway testing in line with the guidance. The fifth site has changed its postpartum care pathway so that cord blood testing is only done when the NIPT result for fetal *RHD* genotype is negative, to confirm the D-negative result. See [section 4.24](#) of the diagnostics guidance.

The committee recommended further research on the practicalities of implementing alternative postpartum-testing strategies.

Measuring success

In order to show the cost and clinical benefit of adopting high-throughput NIPT for fetal *RHD* genotype, it is important to record a baseline assessment and take measurements during and after implementation. These measures should reflect the variables used in the NICE resource impact template.

One site that recently implemented the technology shared the results of the first audit covering the first 6 months after implementation. Results show that of 352 cfDNA tests, 123 were negative, 210 positive and 15 inconclusive; 4 samples were rejected. This means that 35% of D-negative pregnant women in this group would not need RAADP or anti-D immunoglobulin and a Kleihauer test to measure the amount of fetal haemoglobin in

maternal blood after a potentially sensitising event. To date, 143 women have delivered and all 48 babies predicted by ffDNA to be D-negative have had this result confirmed.

Sites involved in developing this resource suggested the following measures of success, and advised that the implementation team decide locally who is responsible for collating and managing this data:

- number of anti-D clinic appointments used
- amount of anti-D immunoglobulin ordered on an annual basis
- amount of anti-D immunoglobulin used calculated as a percentage of the number of babies delivered and repeated at specified time points
- rate of uptake of the test (percentage having test of those offered)
- qualitative feedback from midwives on confidence in and understanding of the new process through an anonymised survey
- proportion of D-negative women with an ffDNA-negative result
- number of Kleihauer tests done
- rates of true positive and true negative results.

Some maternity services routinely record data centrally, which can be used to look at some of the above measures. Suggested data include:

- booking date
- estimated date of delivery (EDD)
- mother's D status
- whether a ffDNA test has been done
- cord blood test result
- potentially sensitising events
- baby's hospital identification number
- anti-D immunoglobulin administration.

Clinicians who are considering further research please cross reference with research recommendations [6.1](#) and [6.2](#).

Education and communication plans

Training should mainly focus on raising awareness of the change to the current care pathway. Literature, midwife information leaflets, patient information leaflets, and a list of frequently asked questions are available from NHSBT to help develop training packages.

- Identify which staff groups need to be trained, what they need to know how training will be delivered and where it will be done, in order to increase the number of staff trained.
- Identify the most appropriate person to provide the training, such as a suitably qualified practice development midwife with input from transfusion practitioners.
- Training should include the following main two stages:
 - sample taking and acting on the fetal *RHD* genotype result **and**
 - cross checking the cord blood test result with the fetal *RHD* genotype result.
- Include the importance of correct labelling and documenting the expected delivery date, to avoid sample rejection and ensure the result can be linked to the woman's correct pregnancy episode.
- Provide information packs for all midwives to include information leaflets, local policy, sample request forms, contact details for clinical support, and sample result letters.
- Include training on high-throughput NIPT for fetal *RHD* genotype in the anti-D update sessions as part of the annual midwifery training programme.
- Identify a local champion for staff to contact if they have questions.
- Include laboratory staff, general labour ward staff, consultant obstetricians and gynecologists, and GPs in the training plan.

- Provide written information for women, either by paper or electronic leaflets, or a maternity mobile application, if available locally. One site provides extra information to midwives with more explanation about the risk associated with a test result that shows a D-negative fetus, but at birth the baby is then confirmed as D-positive, that is, a false-negative test.

A communication plan should include:

- Implementation planning – develop strategies for informing all staff groups of the planned implementation. The contributing sites:
 - identified midwife champions at each point of the maternity pathway
 - sent the new guidelines to each midwife directly and circulated them with monthly forum minutes
 - displayed promotional posters in antenatal midwife offices
 - discussed strategies with maternity colleagues whenever possible
 - developed local information for women.
- Pre implementation – provide reminders to staff in the weeks leading up to the implementation date.
- Intrapartum care – plan for refresher communications at 4 months and 6 months after implementation, for the staff who will care for the women at the time of delivery. The laboratory or maternity team will have a record of the expected date of delivery for the women who were tested.

Developing local documentation

Contributors to this resource advised that the implementation team should ensure local processes and care pathways are documented in a local guideline. Sharing this with clinical staff at draft stage is important to identify possible issues with implementing the suggested process. Sites report that showing the pathway as a flowchart is helpful for clinical staff. The following are examples of tools developed by NHS services using high-throughput non-invasive prenatal testing for fetal *RHD* genotype, which can be used for developing local documentation. They have not been produced, commissioned or endorsed by NICE:

- Harrogate and District Hospital NHS Foundation Trust:
 - [Fetal Rh Status test – poster](#)
 - [Fetal Rh midwife information and process map](#)
 - [Fetal Rh \(Patient\) test letter](#)
- Taunton and Somerset NHS Foundation Trust:
 - [Guidelines for the use of anti-D for the prevention of haemolytic disease of the fetus and newborn](#)
 - [cffDNA flow chart](#)
 - [cffDNA test result label sheet for notes](#)
- University Hospitals Bristol NHS Foundation Trust:
 - [Guideline – Rhesus \(RhD\) negative antenatal management](#)

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7 About this resource

This resource accompanies NICE diagnostics guidance on [high-throughput non-invasive prenatal testing for fetal RHD genotype](#). It was developed using the NICE's [process guide for adoption support resources for health technologies](#). It is an implementation tool and discusses and summarises the experiences reported by NHS sites which have adopted this technology and shares the learning that took place.

It is the responsibility of local commissioners and providers to implement the guidance at a local level, being mindful of their duty to advance equality of opportunity and foster good relations. Nothing in this document should be interpreted in a way that would be inconsistent with this.

[More information about the adoption team.](#)

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