NHS
Blood and Transplant

International Blood Group Reference Laboratory (IBGRL)

Molecular Diagnostics

The future of antenatal care

Index

Summary

Non-invasive prenatal testing (NIPT) using cell free fetal DNA in maternal plasma can be used to determine fetal D blood group antigen status so that D negative pregnant women can avoid receiving antenatal anti-D if they are carrying a D negative baby.

The test has been implemented in several hospitals throughout England and Ireland, and as a national test in some European countries.

This low cost, highly accurate test is now available to all hospital trusts in the UK and Ireland via NHS Blood and Transplant.

Current practice is to provide antenatal anti-D prophylaxis at 28-30 weeks gestation, which means that about 40% of healthy D-negative pregnant women are exposed to a pooled human blood product that they do not need as their baby is D negative.

NIPT allows health services to conserve the use of a costly product that can be in short supply and permits targeted anti-D prophylaxis for those women who may benefit from it.

Key points

- The NICE recommendation for high-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* has been published on their website as a cost-effective option to guide antenatal prophylaxis with anti-D immunoglobulin (anti-D Ig)> For further information see https://www.nice.org.uk/guidance/dg25
- The current practice of giving anti-D Ig to all D negative pregnant women means up to 40% of women receive this human blood product when they do not need it.
- A non-invasive fetal DNA test is now available within the NHS to predict the fetal D group from 11+2 weeks gestation.
- The test is highly accurate and can be used to target anti-D Ig administration to women who may benefit from it (both at 28 weeks gestation and for potentially sensitising events during pregnancy)
- Use of this test to guide anti-D Ig administration in routine maternity care has been implemented within the NHS, and this approach has proved popular with midwives and pregnant women.
- This approach has the potential to provide a cost-saving in maternity service budgets.

The International Blood Group Reference Laboratory

– an established reference centre for red cell diagnostics

Our History

Reference c. 1955

The Blood Group Reference Laboratory (BGRL) was established in 1946 when it was housed in the Lister Institute in Chelsea, England. Its two main functions were to provide a centralised service for the production of blood grouping reagents and to provide a red cell reference service to the newly formed National Blood Transfusion Service. In 1953 BGRL gained World Health Organisation (WHO) recognition for its red cell reference work and became the International Blood Group Reference Laboratory (IBGRL).

Always at the forefront of blood group research and development, IBGRL established a clinical service to predict the blood group status of fetuses at risk from haemolytic disease of the fetus and newborn (HDFN) in 1994 using fetal DNA derived from amniocytes or chorionic villus. In 2001 IBGRL became the first laboratory to offer a clinical non-invasive prenatal test (NIPT) for fetal D blood group using cell free fetal DNA in maternal plasma.

Now

2016

IIBGRL is now part of NHS Blood and Transplant, located at the Bristol site and served by the national NHSBT transport network. IBGRLs Molecular Diagnostics department offers blood group genotyping to provide molecular typing support for routine maternity and transfusion services both nationally and internationally. The department offers a rapid, non-invasive, convenient and reliable service for prediction of fetal D, C, c, E and K status, using cell-free fetal DNA in maternal blood for women who have allo-antibodies.

IBGRL have optimised and automated this testing technology applied to pregnancies at risk of HDFN to enable sufficient high throughput testing to perform fetal *RHD* screening of all D-negative pregnant women, who have not formed immune anti-D or anti-G[3].

Scientific advances instigate changes

Anti-D immunoglobulin (anti-D Ig) prophylaxis has been a highly successful example of preventative medicine. It has reduced the incidence of sensitisation of pregnant women to the D antigen and thus haemolytic disease of the fetus and newborn (HDFN)[1]. The current policy[2] of giving antenatal anti-D Ig means that almost 40% of D-negative pregnant women (approximately 40,000 women per year in England) receive antenatal anti-D Ig in pregnancy unnecessarily, because they are carrying a D-negative fetus. In the 2008 guidelines on routine antenatal anti-D Ig prophylaxis (RAADP) NICE recommended further research into large scale automated NIPT suitable for testing all D negative women.

Several trials have been carried out at IBGRL to investigate the performance of the fetal *RHD* screening test. A National Institute for Health Research (NIHR) funded multi-centre study[4] investigated test sensitivity at different gestational ages and concluded that the test is reliable from 11^{+2} weeks gestation.

Implementation pilot

Following the NIHR study, a service implementation pilot was undertaken in the south-west of England to identify potential difficulties in clinical practice and assess how easily they could be overcome in the NHS.[5] The pilot demonstrated that it is possible to implement routine NIPT in D-negative women in the NHS. The requirements of patient information, consent, sample handling, result transfer and implementation of the changed management for anti-D Ig administration were all successfully met.

The experience within British maternity services has been very positive. The implementation of the new protocol has been well accepted by both maternity staff and pregnant women, without additional funding or resources.

The implementation of the test has allowed anti-D Ig to be used in a more precise and indicated way in Trusts adopting this approach, and the cost of the test can be resourced by the saving in anti-D Ig. Several publications in British obstetric and midwifery journals have described the service implementation pilot within the NHS.[5,6]

International

National fetal *RHD* testing programmes for all D-negative pregnant women have been introduced successfully in other countries (Denmark, Netherlands, Finland, parts of Sweden).

NICE recommendation

The NICE recommendation for high-throughput non-invasive prenatal testing (NIPT) for fetal *RHD* has been published on their website as a cost-effective option to guide antenatal prophylaxis with anti-D immunoglobulin (anti-D Ig). For further information see https://www.nice.org.uk/guidance/dg25.

Fetal *RHD* Screening test

The test offered by NHS Blood and Transplant can improve antenatal care for all D-negative women in the UK and Ireland.

The current practice of giving a blood product that is pooled from multiple donors to healthy pregnant women, is undesirable, unethical and unnecessary.

Key benefits

- IBGRL Molecular Diagnostics is a UKAS accredited medical laboratory (number 9765) offering the fetal *RHD* screening service to prevent unnecessary administration of anti-D Ig prophylaxis
- Prediction of fetal D blood group from 11+2 weeks gestation onwards
- The test offers >99.9% negative predictive value. Fewer than 1:1000 babies will be falsely predicted to be D negative if the test is performed after 11+2 weeks gestation.
- Tailored to the needs of maternity and transfusion services
- Results are available via the NHSBT electronic reporting system – Sp-ICE
- Sp-ICE provides vital information to obstetricians and midwifes even if the pregnant women has not been booked at your hospital.
- The test enables obstetric teams to focus on women carrying a D-positive fetus
- Reduces anti-D Ig administration by as much as 40%
- Reduces need for laboratory tests i.e. feto-maternal haemorrhage estimation and cord blood group testing
- Maximises bed capacity - enabling midwifes to give anti-D Ig immediately to mothers of D positive babies
- Supply of patient information leaflets – included in the cost of the test to support informed consent
- Use of NHBST transport network at no additional cost (for NHS Trusts only).

Price: Please contact Molecular Diagnostics – email: molecular.diagnostics@nhsbt.nhs.uk

The cost of the test is offset by:

- Reduction in administration of anti-D Ig at 28 weeks
- Reduction in administration of anti-D Ig for potentially sensitising events in pregnancy
- Decrease in associated requests for feto-maternal haemorrhage estimation tests
- Maximising bed capacity - enabling midwives to give anti-D Ig immediately to mothers of D positive babies.

Test restrictions

1. This service is only available to Trusts who have signed a contract and FRM5578 for this service with NHSBT.
2. This is not a diagnostic test for the fetal D status of women who have made allo-immune anti-D or -G (an alternative test is provided for allo-immunised women at IBGRL, see http://ibgrl.blood.co.uk).
3. The test has been designed to minimise false D negative results to <0.1%. Fewer than 1:1000 women predicted to be carrying a D negative fetus will therefore not receive anti-D during pregnancy when they may have benefited from it but should still receive post-natal prophylaxis if guidelines are followed.
4. In up to 2% of tests the result will be incorrectly predicted to be D positive despite the baby in fact being D negative[7]. This small false positive rate when using the NIPT, means that only 2% of D negative women receive antenatal prophylaxis unnecessarily, rather than 40% without using the NIPT.

What do I need to know about the service?

Ethics

Although anti-D Ig has been an exceptionally safe product, which should be strongly recommended to those women with a D-positive fetus, conditions such as prion disease and other as yet unknown factors should continue to make us ensure blood products are used only when needed.

Irrespective of the financial costs or benefits, it is unnecessary to continue administering a blood product to all D-negative women when a fetal *RHD* genotyping test, using maternal blood, could identify those women who do not need this product.

In addition, the availability of anti-D Ig, a human derived pooled product, is limited and requires deliberate sensitisation of volunteers. Both the difficulties of availability and the theoretical risks mean it should be used only when required.

Accuracy

The overall accuracy and particularly the sensitivity of the fetal *RHD* screening test is very high. There is approximately <0.1% likelihood of a fetus being incorrectly predicted to be D-negative. When fetal *RHD* screening is performed the proportion of women, who will be recommended to receive antenatal anti-D Ig unnecessarily, is just 2% (compared to about 40% without fetal *RHD* screening)[7].

Incorrect prediction of a fetus to be D-positive can occur when a variant *RHD* gene is present in the fetus or the mother, or when test results are inconclusive, in which case anti-D Ig administration is recommended. This is because it is the safest option, and some individuals can possess an *RHD* gene, but their blood group is D negative. In a previous study, 77% of the women with inconclusive test results gave birth to D-positive fetuses[5]. Refinement of the test will continue, and it is possible that the rate of inconclusive test results will be reduced in the future.

Transport and reporting

Samples should be sent at room temperature and must be received at NHSBT in Bristol within 7 days of venepuncture.

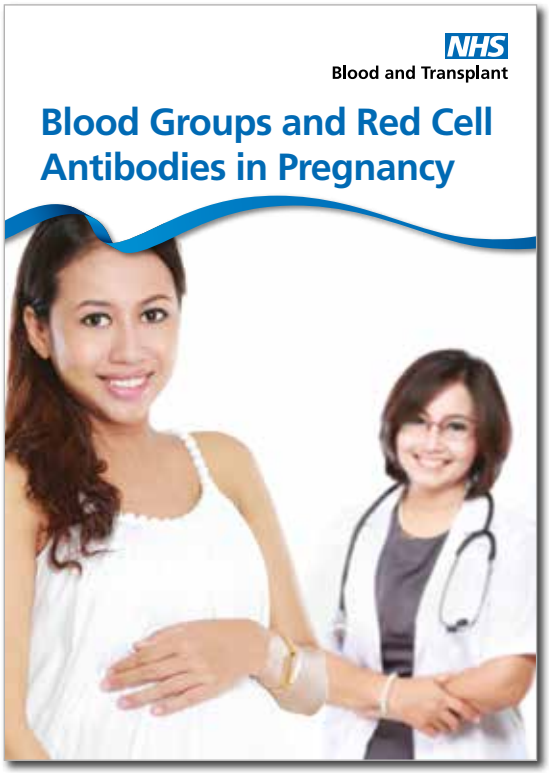
NHSBT transport is used to transfer samples from NHS pathology laboratories within the specified time via our established routine rounds. Trusts outside NHSBT's logistic network will send their samples by 1st class post.

The upper turnaround time for the fetal *RHD* screening test is currently 14 days with target average turnaround time of 5 days from sample receipt. This is likely to be reduced once an increased volume of samples is being analysed.

All results are available via Sp-ICE, the electronic NHSBT reporting system, which enables hospitals to have direct access to reports on-line. This supports better transfusion therapy in the event of shared care or delivery at another hospital.

Patient information leaflets and other documents

NHSBT has developed a user guide, patient information leaflet and request form to support midwives, pathology and obstetric staff.



Both leaflets are available from the website: https://hospital.blood.co.uk/

Success stories

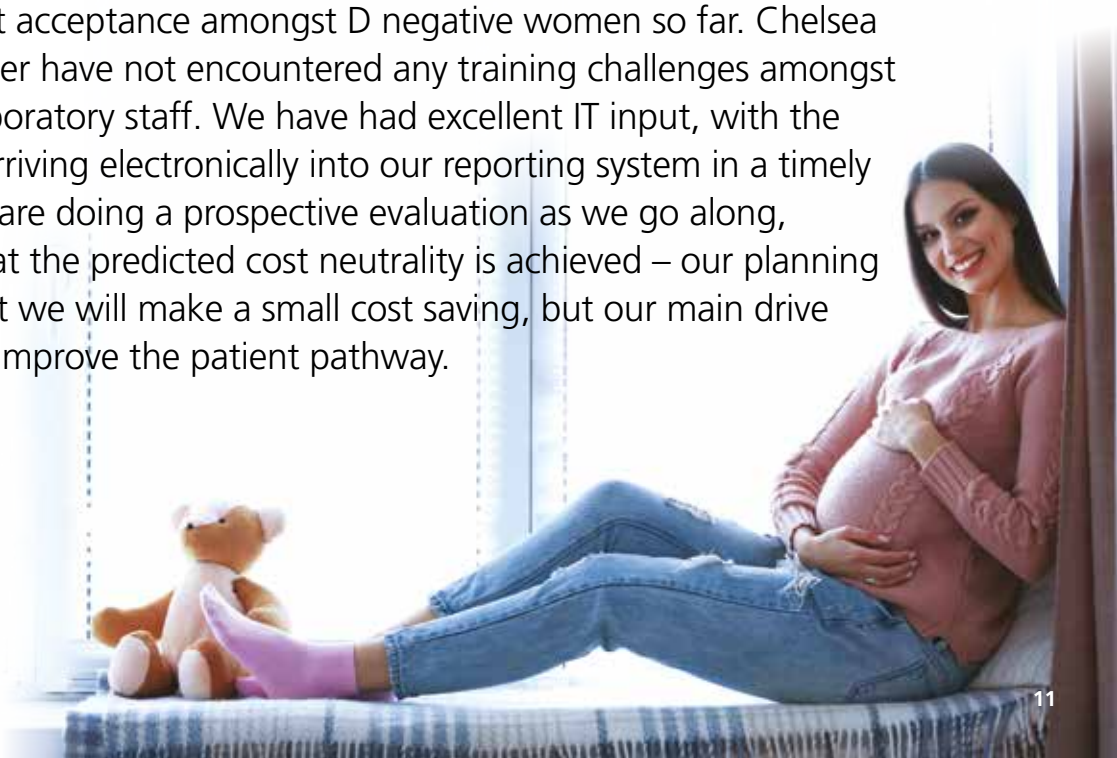
1. **Yeovil** – Midwives and pregnant ladies are very pleased with the newly introduced service.

2. **Oxford** – Our patient had her blood sent to IBGRL on Friday 5th and presented to us on Thursday 11th with a bleed. The midwives in the assessment unit rang to see if I could help get her results. I am pleased to say I was able to look them up on your Sp-ICE system and see they had been reported the previous day. What a turnaround, our patient was especially pleased as her baby is predicted to be D negative.

3. **Harrogate** – Midwives are pleased with the turnaround times despite the fact that the samples have to go via Leeds, Manchester and Birmingham to reach Filton. Average turnaround from sample taken at the clinic to receipt of result on the ward is only 9 days.

   The prompt turnaround time has also helped with the decision making for some women nearing their 28-30 week prophylactic anti-D Ig where they were unsure whether to refuse or not. Whenever we have had a query or required more information the response from the IBGRL team has been really helpful.

4. **Chelsea & Westminster Trust** – Introduced the fetal *RHD* screening test in June 2016 and are following the pathway with cord testing on fetuses predicted to be D negative or with inconclusive results. We have had excellent acceptance amongst D negative women so far. Chelsea & Westminster 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.



Fetal *RHD* screening – Questions and Answers

Q: Can the test be used for women who expect multiple births?

A: Yes, we can test women pregnant with twins / triplets, but the report will predict the (single) fetus as being positive or negative. A positive result in this case means **at least one** of the babies is D positive. A negative result would mean that all of the babies are D negative.

Q: What is the percentage of D negative women who will have an D negative baby?

A: The prevalence of D negative women in a Caucasian population is 15% of which 38% to 40% will have D negative babies. However, these figures will differ depending on the ethnic diversity of the local population, which may make a difference when calculating cost savings for implementation of the test.

Q: What is the percentage of women who are D negative and have a D positive baby who produce anti-D when they do not receive anti-D Ig?

A: The usual figures quoted are 1% women become sensitised if they receive post-natal anti-D but do not receive antenatal anti-D at 28 weeks. Sensitisation is reduced to 0.35% with the addition of routine antenatal anti-D prophylaxis (RAADP).

Q: What is the failure rate of anti-D Ig?

A: Apart from the failure to administer a correct dose at the correct time, the failure rate is quoted as 0.37% (NICE Health technology assessment 2003). See Table below taken from the NICE assessment for implementation of the fetal *RHD* screening test.

Clinical effectiveness of RAADP and postpartum anti-D prophylaxis

	Odds ratio: sensitisation with RAADP[1] (95% CI)	Odds ratio: sensitisation at birth, follow-up up to 6 months, with postpartum anti-D prophylaxis[2] (95% CI)	Sensitisation rate without RAADP[3] (95% CI)	Sensitisation rate with RAADP (95% CI)	Sensitisation rate without RAADP and without postpartum anti-D prophylaxis (95% CI)
NICE TA156 (2009)	0.37 (0.21 to 0.65)	–	0.95 (0.18 to 1.71)	0.35 (0.29 to 0.40)	–
Crowther et al. (1997)[4]	–	0.08 (0.06 to 0.11)	0.95[5] (0.18 to 1.71)	–	10.7 (8.0 to 13.8)

1 Versus no RAADP, conditional on having postpartum anti-D prophylaxis.
2 Versus no postpartum anti-D prophylaxis, conditional on no RAADP.
3 Conditional on having postpartum anti-D prophylaxis.
4 Sensitisation 6 months after delivery.
5 Baseline-sensitisation rate of no RAADP assumed the same.

Abbreviations: CI, confidence interval; RAADP, routine antenatal anti-D prophylaxis.

Q: What is the official quoted figure for the risk of transmission of infection with anti-D Ig?

A: There has never been a transmission of infection from anti-D Ig in the United Kingdom. There have been two episodes of transmission of Hepatitis C decades ago, in the Republic of Ireland and Germany; both were prior to the introduction of modern modes of testing and pathogen inactivation, which would have prevented them. Transmission is effectively zero with the current products. However, unknown agents (like vCJD) should be considered in any risk assessment. Check the anti-D Ig manufacturer's product information leaflet for current information on risk of infection.

Q: What is the risk of acute adverse [anaphylactic] reaction?

A: You would need to contact the individual manufacturers of each specific anti-D product, as it will vary depending on the preparation of the anti-D Ig. However, the risk should be considered as very low.

Q: With the fetal *RHD* screening test leaving the pilot phase and national roll out, can hospitals drop the testing of cord blood for D at delivery when the result of the test states the baby will be D negative?

A: NHSBT are not currently recommending that hospitals discontinue cord blood testing at this time, although the cord blood test for predicted D positive babies could be suspended.

Other European countries have continued cord blood testing for several years post introduction of the national screening test. (See above questions on sensitisation and anti-D Ig failure rates). However, Denmark and the Netherlands have discontinued cord blood testing.

Q: Can samples be tested when pregnant women have alloantibodies other than anti-D and anti-G?

A: Yes, samples can be tested for fetal *RHD* in the screening test, which establishes the predicted D status of the fetus. Other alloantibodies like anti-E, anti-C, anti-K etc do not influence the accuracy of the test.

Q: Can samples be tested when pregnant women have already received Anti-D Ig?

A: Yes, samples can be tested for fetal *RHD*. The anti-D Ig does not interfere with this test.

What other tests are available from IBGRL Molecular Diagnostics?

Our services

- **Fetal *RHD* screening test**

  A fetal *RHD* screening service to prevent unnecessary administration of anti-D Ig prophylaxis. The test predicts fetal D status with high accuracy from a sample of maternal blood and will improve care for D-negative women by reducing the need to administer a blood product to healthy pregnant women.

- **Fetal blood group genotyping**

  Prediction of fetal D, c, C, E blood groups from 16 weeks and Kell (K1) from 20 weeks gestation. Identifying women with antigen-positive fetuses for further careful monitoring during their pregnancy. It will also identify pregnant women who have antigen-negative fetuses and are, therefore, not at danger from HDFN. If these women are identified, further invasive procedures can be avoided.

- **Paternal zygosity in relation to *RHD* fetal genotyping cases**

  This test determines whether the father has 1 or 2 copies of the *RHD* gene, which is useful in the planning of future pregnancies.

- **Fetal sex genotyping**

  For pregnancies affected by X-linked genetic conditions or when early treatment of the fetus differs according to fetal gender. Samples can be accepted from 7 weeks gestation.

- **Blood group genotyping***

  Providing blood group genotyping for multiply transfused patients. Experience in offering blood group genotyping for both national and international users for over 20 years to assist unit selection for blood transfusion.

  - **Standard blood group genotype** D, C, c, E, e, K/k, $Fy^{a/b}$, $Jk^{a/b}$, M/N, S/s, U-, U^{var}
  - **Extended blood group genotyping** which includes standard genotype plus V, VS, Fy^{X}, $Kp^{a/b}$, $Js^{a/b}$, $Lu^{a/b}$, $Di^{a/b}$, $Co^{a/b}$, $Do^{a/b}$, $LW^{a/b}$, Sc
  - **Extended blood group genotyping (haemoglobinopathy array):** D, C, c, E, e, (including common RhD, C and e variants),V, VS, hr^{B}, hr^{S}, K/k, $Kp^{a/b}$, $Js^{a/b}$,$Do^{a/b}$, $Fy^{a/b}$, $Jk^{a/b}$, M/N, S/s, U-, U^{var}
  - **ABO blood group** may be requested – please note that any clinical decisions relating to transfusion and transplantation must not be made on the basis of the ABO group predicted from these results.

Standard patient genotyping requests can be performed more quickly than the normal turnaround time, if required, for an added premium, provided that the sample is received by mid-day Monday to Friday before testing is required.

*Tests listed are correct at time of printing, please check with the laboratory for current list of genotypes available.

We can also support you with the following information when you contact us:

- Examples of Maternity pathways led by either clinical or laboratory based teams
- A calculation template to assess your cost (savings)
- Question and Answer document
- Business plan support.

Further support from our Business Development Manager is available, please contact:

Erika Rutherford
Mobile: 07808 906398
Email: erika.rutherford@nhsbt.nhs.uk

See details on the IBGRL website
https://ibgrl.blood.co.uk/

IBGRL Contact Details

Address:

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NHS Blood and Transplant,
500 Northway,
North Bristol Park,
Filton,
Bristol BS34 7QH.

Email: molecular.diagnostics@nhsbt.nhs.uk

Please visit our website to access the relevant departments' user guides, which contain our current contact details and information regarding referral of samples.

https://ibgrl.blood.co.uk/

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NHS Blood and Transplant

NHS Blood and Transplant (NHSBT) saves and improves lives by providing a safe, reliable and efficient supply of blood and associated services to the NHS in England. We are the organ donor organisation for the UK and are responsible for matching and allocating donated organs. We rely on thousands of members of the public who voluntarily donate their blood, organs, tissues and stem cells.

For more information

Visit https://hospital.blood.co.uk/
Email customer.services@nhsbt.nhs.uk
Call 01865 381010

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INF1481/1.1 Effective date: 24/06/22 2223150