
International Blood Group Reference Laboratory (IBGRL)

IBGRL, a UKAS accredited medical laboratory (number 9765), provides specialist diagnostic services in NHS Blood and Transplant (NHSBT). All work carried out in the Molecular Diagnostics department is within the framework of a documented quality system; please refer to the [licensing and accreditation](#) section of our website. The department participates in external quality assurance exercises for blood group genotyping.

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General information:

Terms and conditions

Please see our website for terms and conditions when referring samples to IBGRL Molecular Diagnostics. Referral of samples accompanied by a signed and completed Molecular Diagnostic request form and acceptance of this sample for testing by the laboratory constitutes an agreement between the Requester and NHS Blood and Transplant as outlined in the terms and conditions. Verbal requests for testing are not accepted.

Please note that if your Trust or hospital has signed a service level agreement (or agreement under Schedule 8 of the Contract for the Supply of Blood, Blood Components and Services) with NHS Blood and Transplant, then that agreement will supersede the terms and conditions referenced above and a signature on the referral form is not required.

Laboratory contact details

For enquiries, please contact the IBGRL Molecular Diagnostics laboratory. Requests for clinical advice will be referred to the relevant NHSBT consultant haematologist or clinical scientist.

Tel: +44 (0)117 921 7572 Email: molecular.diagnostics@nhsbt.nhs.uk

Website <https://ibgri.blood.co.uk/>

Laboratory address (postal address for samples):

Molecular Diagnostics
International Blood Group Reference Laboratory
NHS Blood and Transplant
500 North Bristol Park
Northway, Filton, BS34 7QH

Normal working hours: Monday to Friday 07:00-18:00, Saturday (limited service available) 07:00-16:00. Telephone enquiries Monday – Friday 09:00 – 17:00 (answerphone outside these hours)

Pricing and Request Forms

Please contact the laboratory for current pricing information and request forms.

Customer complaints and suggestions

IBGRL Molecular Diagnostics is committed to continuously improving the quality and range of services provided and welcomes any comments or suggestions from users. Please contact the Laboratory Manager or Head of Department in the first instance regarding complaints and suggestions. Complaints are managed via our Quality Management system or Customer Services as appropriate. We always strive to provide a satisfactory response to any complaint. In the unlikely event that your complaint is not resolved to your satisfaction please refer to the NHSBT complaints procedure <https://hospital.blood.co.uk/commercial-and-customer-service/complaints-compliments-and-feedback/>

Data protection / privacy assurance / consent for genetic testing

All information provided to NHS Blood and Transplant is used in accordance with the General Data Protection Regulation and all other relevant privacy and data protection laws. To find out more about your privacy rights please visit our website <https://www.nhsbt.nhs.uk/privacy/>. Staff access to the patient information is on a need-to-know basis for clinical care purposes only and patient confidentiality is respected at all times.

All genetic testing requires informed consent. It is the responsibility of the test requester to ensure that appropriate patient consent has been obtained. The laboratory assumes that, on receipt of a clinical sample and a completed referral form, consent for genetic testing has been obtained. Where appropriate, extracted DNA is stored for NHSBT quality assurance purposes or service development within NHSBT. Genetic material is not distributed outside of NHSBT unless specific informed consent from the individual is obtained.

Fetal D, c, C, E and K blood group determination and fetal sex genotyping from maternal blood

Introduction

Cell-free fetal DNA is normally present in maternal blood plasma throughout pregnancy (Lo *et al*, 1998). This DNA can be analysed following maternal venepuncture, without risk to the fetus, and molecular techniques can be used to predict blood group status or gender of fetuses at risk of haemolytic disease of the fetus and newborn (HDFN) or X-linked genetic conditions respectively. The amount of fetal DNA in maternal blood increases throughout gestation. At early stages of pregnancy, the amount of fetal DNA may be too low to detect. The amount of fetal DNA in maternal blood generally increases throughout the pregnancy but is rapidly cleared from the mother's blood following birth.

Technical aspects of the testing procedure

Analysis of free fetal DNA in maternal blood relies upon the detection of fetal alleles or genes which are absent in the maternal genome.

Fetal *RHD* Genotyping

There are several genetic causes for the D-negative phenotype. In the majority of Caucasian D-negative individuals the *RHD* gene is absent, however, the majority of D-negative black African individuals carry an intact but non-functional *RHD* gene, termed the *RHD* pseudogene (Singleton *et al*, 2000). Real-time PCR is used to amplify exons 4, 5, 7 and 10 of the *RHD* gene in order to distinguish the expressed *RHD* gene from the most common non-expressed or variant *RHD* alleles. However, the molecular biology of the Rh system is incompletely understood and due to its complexity and ethnic diversity, there remains the possibility that on very rare occasions, genotyping results may not correspond to phenotype by conventional serology. Clinical decisions should not, therefore, rely solely upon genotyping results.

Genotyping for other blood groups

The molecular bases of most blood groups associated with HDFN are known and real-time PCR is used to target blood group alleles that are not present in the mother's genome and thereby to predict the blood group status of her unborn baby.

Fetal Sex Typing

This test uses real-time PCR to amplify DNA sequence (*DYS14*) located on the Y chromosome.

Limitations of Non-Invasive Genotyping

Please note that we cannot confirm the presence of fetal DNA in a maternal blood sample. There is a possibility that failure to detect the fetal gene of interest may be due to undetectable levels of fetal DNA in the sample and may not indicate that the fetus is negative for that blood group or lacks the Y chromosome. There is a theoretical possibility that in a very small number of pregnancies we may detect fetal DNA from a fetus that has subsequently been lost as a result of the 'vanishing twin' phenomenon (Landy & Keith, 1998). In addition, due to the complexity of some blood group systems, there remains the possibility that on very rare occasions, genotyping results may not correspond to phenotype by conventional serology. Measurement uncertainty for the assays used in the laboratory has been established and is available upon request.

Referral of maternal blood samples

Gestational age (see Transport of Samples section for time sensitivity of sample receipt)

Requests for fetal D, c, C and E genotyping are accepted from 16 weeks gestation. In some circumstances we will test samples before the recommended gestation (please contact the laboratory to discuss). In such cases, where a negative blood group is predicted, we recommend that another sample is sent after 16 weeks gestation, and both tests will be chargeable.

Requests for fetal K genotype are only accepted from 20 weeks gestation, requests prior to 20 weeks will be rejected. Unless the fetus is found to be K-positive, the report will carry a recommendation to send a repeat sample after 28 weeks gestation. A K-negative prediction will only be reported when a confirmatory sample has been tested after 28 weeks gestation and found to be K-negative. Both tests will be chargeable. It is recommended that pregnancies with anti K antibodies should continue to be monitored by Doppler ultrasound until the results of the second confirmatory sample have been obtained.

Requests for fetal sex prediction can be sent from 7 weeks gestation.

Sample and request form requirements

It is the responsibility of the test requester to ensure that patient consent has been obtained.

16ml maternal blood in EDTA tubes **per test requested**.

3ml paternal blood sample should be sent, if available, when requesting fetal D status. A paternal sample is not essential for most fetal D status requests but can help to establish the presence of a variant *RHD* gene in the fetus.

The sample tubes must not be opened following blood collection or used for any testing prior to being sent to IBGRL.

The sample tubes should be stored at room temperature prior to reaching the laboratory and must not be lysed on receipt.

Samples **MUST** be labelled, dated and signed by the person taking blood.

Labels pre-printed prior to phlebotomy e.g. addressograph labels, are not acceptable on samples. They are, however, acceptable on request forms providing they do not obscure other vital details

Samples must have handwritten labels unless demand printed labels are produced at the time of phlebotomy. NHSBT must be informed in writing if demand printed labels are in use.

A request form must accompany every sample and must be signed by the requester (please see Terms and Conditions section for signature requirement).

Please complete the appropriate referral forms

- [FRM4674](#) for fetal blood group genotyping from maternal blood
or
- [FRM4739](#) for fetal sex typing from maternal blood

Instructions for completing [FRM4674](#) and [FRM4739](#) are detailed in [INF1343](#) and [INF1342](#) respectively, available on the website <http://ibgri.blood.co.uk>

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Request forms are the basis of the correct identification of the patient.

The points of identification provided on the request form must match the information provided on the sample. The department will not normally accept samples unless three or more identical points of identification are used on both forms and tubes.

Hospital identification (request form)

Please ensure the hospital name is written out in full. Do not abbreviate as this may be misinterpreted and could lead to the report being sent to the wrong location, or the sample may not be tested if the requester cannot be identified.

Minimum patient identification

- Surname/family name and first name(s) in full (surname and first name are one identifier)
- NHS number, hospital number or unique identification number (the same number must be on both the tube and the form)
- Date of birth.

The following information must also be provided:

- Date of venepuncture
- Estimated delivery date (by scan) or gestational age in weeks.

Samples which do not meet the above specification will be rejected at receipt

Preparation of frozen samples

Samples referred from outside the UK can be sent as frozen plasma aliquots prepared to a protocol provided by IBGRL – see [INF1291](#). Please contact the laboratory prior to sending frozen plasma. Frozen plasma aliquots that do not meet the sample labelling requirements listed in [INF1291](#) will not be tested.

Packaging of samples

It is the responsibility of the requester to ensure that all samples are packaged in accordance with the current European agreement concerning Carriage of Dangerous Goods by Road Regulations, and IATA (packaging instruction 650), to prevent breakage or spillage in transit. For all transport purposes, pathogens are assigned according to categories A and B. Unless it is known or reasonably believed to contain infectious substance of category A (e.g. haemorrhagic fevers), all human or animal material is regarded as category B, UN 3373.

Category A

Category A includes higher risk infectious micro-organisms, defined as an infectious substance which is transported in a form that when exposure to it occurs is capable of causing permanent disability, life threatening or fatal disease in otherwise healthy humans or animals.

Category B

Category B includes infectious substances that do not meet the criteria for inclusion in category A, and include human and animal material such as, but not limited to, excreta, secreta, blood and its components, tissue and tissue fluids, and body parts being transported for purposes such as research, diagnosis, investigational activities, disease treatment or prevention. All diagnostic or clinical samples are to be deemed and labelled Biological Substance Category B, UN 3373 and must meet Packaging Instruction 650:

- Primary inner receptacle and secondary receptacle, both must be sealed and leak proof
- Rigid outer packaging (the outer package must also have one side with the minimum dimensions of 100mm x 100mm)

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- All packages must use a visible diamond-on-point label UN3373 (min require dimension of this diamond are 50mm x 50mm)
 - Adjacent to the diamond must be the label 'Biological Substance, Category B' and all text MUST be 6mm in height
 - Packaging Instruction 650 now permits up to 1 litre per primary receptacle with a total of 4 litres per package for liquids and 4kg for solids. Either primary or secondary receptacle must withstand pressure of 95kPa and a 1.2 meter drop test

Transport of samples

Samples must reach the laboratory in time to be processed during laboratory working hours within set time limits after venepuncture. Sample reception is open around the clock, but samples must arrive during working hours Monday to Friday 09:00 to 17:00, so that they can be processed within the time limits below:

- Referrals for fetal K status must be processed within 2 days of venepuncture
- Referrals for fetal D, c, C or E must be processed within 3 days of venepuncture
- Referrals for fetal sexing must be processed within 7 days of venepuncture

Time-dependent samples (especially samples for fetal K status) should not be sent on NHSBT transport but should be sent by first class post or courier. Timing starts on day of venepuncture.

Timing is a guide to suitability of samples for testing, but other factors may affect sample condition (e.g. exposure to fluctuation in temperature, heat, incompletely filled EDTA tubes). Samples which have lysed due to prolonged time or adverse conditions in transit or which are not in the requested anticoagulant will be rejected and the reason for sample rejection will be reported.

Blood samples should be shipped at ambient room temperature.

Aliquots of maternal plasma, processed following the protocol listed in INF1291, should be shipped frozen on dry ice. Samples must be received within 5 days and must be frozen on receipt.

Turnaround time & reports (including sample rejection notification)

Our target is to issue reports within:

- 5 working days from date of sample receipt for fetal sex typing from maternal blood
- 7 working days from date of sample receipt for fetal blood group genotyping from maternal blood.

Urgent samples can be tested more quickly by prior arrangement with the laboratory.

The requester will be notified by email or telephone if a significant delay in reporting is anticipated.

A single report will be posted to the address indicated on the referral form and reports are also available on the [Sp-ICE reporting system](#).

Additional requests

Maternal plasma samples will be archived for one year from date of receipt. Additional requests for testing may be made within six months of the first request, subject to there being sufficient plasma to complete the additional test request. If there is insufficient plasma, a new sample must be sent. Additional test charges will apply in either case.

Our requirements of the requester

In order to ensure the standards of our service are maintained and to aid improvement, we try to monitor the accuracy of our testing procedures. We appreciate receiving information on the infant's blood group or sex after delivery. **If there is a discrepancy between the baby's phenotype at birth**

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and the predicted phenotype or baby's sex, please inform the IBGRL laboratory as soon as possible by email: molecular.diagnostics@nhsbt.nhs.uk or by telephone 0117 921 7572. Please retain a sample of cord and maternal blood and send to the Molecular Diagnostics laboratory for investigation.

If samples are referred for fetal D, C, c or E genotyping or sexing before the recommended gestation, and an antigen negative or female gender result is predicted, the requester should send a repeat sample after the recommended gestational age. This will reduce the small chance of an incorrect fetal genotyping result during the pregnancy.

References

Lo YM, Tein MS, Haines CJ, Leung TN, Poon PM, Wains Johnson PJ, Chang AM, Hjelm NM. (1998) Quantitative analysis of fetal DNA in maternal plasma and implications for non-invasive prenatal diagnosis. *Am. J Hum. Genet.* 62:768-775.

Singleton BK, Green CA, Avent ND, Martin PG, Smart E, Daka A, Narter-Olaga EG, Hawthorne LM, Daniels G. (2000). The presence of an RHD pseudogene containing a 37 base pair duplication and a nonsense mutation in Africans with the RhD-negative blood group phenotype. *Blood*, 95:12-18.

Landy HJ and Keith LG (1998) The vanishing twin: a review. *Human Reproduction Update* 4(2):177-183

Blood group genotyping from blood sample or other tissue (e.g. amniotic fluid or chorionic villus)

Introduction

In multi-transfused patients or DAT positive patients, the presence of transfused red cells or auto-antibodies can prevent determination of blood group phenotype by serological techniques, however analysis of DNA can be used to predict blood group phenotype. Where non-invasive cell-free fetal DNA assays are not available, the blood group phenotype of a fetus can be determined by analysis of DNA derived from fetal cells in amniotic fluid or chorionic villus (CV). IBGRL Molecular diagnostics uses various techniques to determine blood group genotype: allele-specific PCR, real-time PCR (allelic discrimination using Taqman probes) and HEA Beadchip. The technique used will depend on the test requested and the current workload in the laboratory.

If resolution of a suspected variant allele /phenotype is required, it is likely that referral to IBGRL Red Cell Reference is appropriate, and a different referral process is required. Please see [IBGRL Red Cell Reference](#) User Guide (INF1136) for details.

Accredited tests & External Quality Assurance – please note the *RHD* Zygosity and Extended Genotype: Haemoglobinopathy Patient Array tests are not currently within scope of the laboratory's ISO 15189 accreditation. The laboratory participates in a NEQAS scheme for blood group genotyping and participates in the HEA Beadchip EQA scheme provided by the College of American Pathologists.

Available genotyping tests (please request the current price list for costs)

STANDARD BLOOD GROUP GENOTYPE (does not detect the presence of D, C or e variants)

D, c, C, E, e, K/k, Jk^a /Jk^b, Fy^a /Fy^b, MN, S/s, U-/ Uvar

EXTENDED BLOOD GROUP GENOTYPE (does not detect the presence of D or e variants)

D, c, C, E, e, V, VS, K/k, Jk^a /Jk^b, Fy^a /Fy^b, Fy^x, MN, S/s, U-/ Uvar, Do^a /Do^b, Js^a /Js^b, Kp^a /Kp^b, Lu^a /Lu^b, Co^a /Co^b, Di^a /Di^b, Sc1/ Sc2, LW^a /LW^b

EXTENDED GENOTYPE: HAEMOGLOBINOPATHY PATIENT ARRAY (a genotyping test array particularly suited for haemoglobinopathy patients). D, C, c, E, e, (including common D, 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 GENOTYPE – *please note that clinical decisions relating to transfusion / transplantation must not be made on the basis of the ABO group predicted from genotyping results.*

RHD ZYGOSITY

This test can be used to determine the *RHD* zygosity of partners of D- women. The tests predict whether the individual carries one or two copies of the *RHD* gene and therefore the likelihood of the fetus inheriting the *RHD* gene. The test can be more accurate than serological techniques to determine *RHD* zygosity, particularly in individuals with the Ro phenotype.

Limitations and caveats

The molecular biology of blood groups, particularly the Rh system, is complex and genetic differences may be found in ethnic groups. It remains a possibility that on very rare occasions, genotyping results may not correspond to serological phenotype. A "positive result" does not preclude the presence of a variant allele / phenotype. Clinical decisions should not, therefore, rest solely on genotyping results.

People who have received a transplant where incomplete engraftment has taken place may exhibit chimerism in their blood cell populations and therefore in their DNA; this may give incorrect

genotyping results or prevent a conclusive result being issued. Clinical history of transplantation should be recorded on the request form.

Measurement uncertainty for the assays used in the laboratory has been established and is available upon request.

Referral of blood samples or other tissues (does not apply to maternal blood for fetal genotyping)

Sample and request form requirements

It is the responsibility of the test requester to ensure that patient consent has been obtained.

Blood. minimum 0.5mL EDTA blood stored at room temperature.

Amniotic fluid. 5ml sample of amniotic fluid should be received within 7 days of sampling. To avoid the possibility of contamination, it is preferable to dispatch the amniotic fluid without transferring it to a second container. If amniotic fluid is transferred from one container to another, then precautions should be taken to avoid contamination with material containing exogenous DNA.

Chorionic Villus. Pre-extracted DNA must be referred. The laboratory performing the DNA extraction should ensure that procedures are in place to prevent contamination of the DNA sample with extraneous DNA or other substances. DNA must be at a minimum concentration of 10ng / μ L and a minimum volume of 60 μ L).

Samples **MUST** be labelled, dated and signed by the person taking the blood.

Labels pre-printed prior to phlebotomy e.g. addressograph labels are not acceptable on samples. They are, however, acceptable on request forms providing they do not obscure other vital details

Samples must have handwritten labels unless demand printed labels are produced at the time of phlebotomy. NHSBT must be informed in writing if demand printed labels are in use.

A request form must accompany every sample and must be signed by the requester (please see Terms and Conditions section for signature requirement).

Please complete referral form

- [FRM4738](#) for standard red cell genotype or extended blood group genotype *(including amniotic fluid or chorionic villus samples)
 - Instructions for completing [FRM4738](#) are detailed in [INF1341](#) available at <http://ibgrl.blood.co.uk>
- [FRM1597](#) Extended Genotype (haemoglobinopathy patient array - particularly suited for haemoglobinopathy patients)
 - Instructions for completing [FRM1597](#) are detailed in [INF417](#) available at <https://hospital.blood.co.uk/diagnostic-services/red-cell-immunohaematology/rci-test-request-form/>

Request forms are the basis of the correct identification of the patient.

The points of identification provided on the request form must match the information provided on the sample. IBGRL will not normally test samples unless three or more identical points of identification are used on both forms and tubes.

Hospital identification (request form)

Please ensure the hospital name is written out in full. Do not abbreviate as this may be misinterpreted and could lead to the report being sent to the wrong location, or the sample may not be tested if the requester cannot be identified.

Minimum patient identification

- Surname/family name and first name(s) in full (surname and first name are one identifier)
- NHS number, hospital number or unique identification number (the same number must be on both the tube and the form)
- Date of birth.

The following information must also be provided.

- Date of venepuncture / sampling

Samples not meeting the above specification will be rejected at receipt.

Packaging of samples

It is the responsibility of the requester to ensure that all samples are packaged in accordance with the current European agreement concerning Carriage of Dangerous Goods by Road Regulations, and IATA (packaging instruction 650), to prevent breakage or spillage in transit. For all transport purposes, pathogens are assigned according to categories A and B. Unless it is known or reasonably believed to contain infectious substance of category A (e.g. haemorrhagic fevers), all human or animal material is regarded as category B, UN 3373.

Category A

Category A includes higher risk infectious micro-organisms, defined as an infectious substance which is transported in a form that when exposure to it occurs is capable of causing permanent disability, life threatening or fatal disease in otherwise healthy humans or animals.

Category B

Category B includes infectious substances that do not meet the criteria for inclusion in category A, and include human and animal material such as, but not limited to, excreta, secreta, blood and its components, tissue and tissue fluids, and body parts being transported for purposes such as research, diagnosis, investigational activities, disease treatment or prevention. All diagnostic or clinical samples are to be deemed and labelled Biological Substance Category B, UN 3373 and must meet Packaging Instruction 650:

- Primary inner receptacle and secondary receptacle, both must be sealed and leak proof
- Rigid outer packaging (the outer package must also have one side with the minimum dimensions of 100mm x 100mm)
- All packages must use a visible diamond-on-point label UN3373 (min require dimension of this diamond are 50mm x 50mm)
- Adjacent to the diamond must be the label 'Biological Substance, Category B' and all text MUST be 6mm in height
- Packaging Instruction 650 now permits up to 1 litre per primary receptacle with a total of 4 litres per package for liquids and 4kg for solids. Either primary or secondary receptacle must withstand pressure of 95kPa and a 1.2 meter drop test

Transport of samples

Samples should be sent by first class post or courier.

Blood samples should be sent at room temperature and received within 14 days of venepuncture.

Amniotic fluid samples should be sent at room temperature and received within 7 days of sampling.

CVS DNA samples may be sent frozen or at room temperature and should be received within 7 days.

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Turnaround Time & reports (including sample rejection notification)

Our target is to issue reports within:

- 10 working days of sample receipt for standard red cell genotype and extended genotype
- 12 weeks of receipt for Extended Genotype Haemoglobinopathy Patient Array - particularly suited for haemoglobinopathy patients to inform non-urgent, future transfusion requirements.

Samples referred for Standard Genotype can be tested more quickly (and within 48 hours if required) by prior arrangement with the laboratory. However, an urgency premium charge (see current price list) will be applied for any sample which is referred with requested turnaround time less than 10 working days from sample receipt.

The requester will be notified by email or telephone if a significant delay in reporting is anticipated.

A single report will be posted to the address indicated on the referral form and reports are also available on the [Sp-ICE reporting system](#). Extended Genotype (haemoglobinopathy patient array) reports are only distributed via Sp-ICE.

Additional requests

DNA samples will be archived for one year from date of receipt. Additional requests for testing may be made within one year of the first request, subject to there being sufficient DNA to complete the additional test request. If there is insufficient DNA, a new sample must be sent. Additional test charges will apply in either case.

Our requirements of the requester

In order to ensure the standards of our service are maintained and to aid improvement, we try to monitor the accuracy of our testing procedures. It is known that genotype does not always reflect phenotype, however, if an unexpected discrepancy between genotype and phenotype is discovered we will be happy to investigate further. Please contact the laboratory to discuss.