Genomic Diagnostics Laboratory
Manchester Centre for Genomic Medicine
6th Floor, St Mary's Hospital, Manchester M13 9WL
Director of Laboratory: Dr E. Howard
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NHS North West
NHS Genomic Laboratory Hub

NW GLH Haemoglobinopathy Diagnostic Service

INDICATIONS FOR GENETIC DIAGNOSIS OF HAEMOGLOBINOPATHIES

Genetic diagnosis for Haemoglobinopathies for the NW GLH is coordinated through the Manchester University Hospitals NHS Foundation Trust (MFT). Criteria for testing are detailed below.

Samples for testing must be labelled with full name, date of birth and NHS / hospital number and should be sent with appropriate referral form which must contain:

1. Full patient demographic details (full name, date of birth, NHS / hospital number and address)
2. Ethnicity
3. Results of phenotypic investigations (e.g. FBC, iron or ferritin levels, HPLC results)
4. Evidence of patient consent – indicated by the signature of the referring clinician on the referral form
5. Referring consultant, contact details and address for report
6. Test requesting 'R' code as stated in the NHS E National Test Directory (see below)

If the referral is for an antenatal patient please send full details of the partner's results and ethnicity, if available.

On receipt of the sample the laboratory will:

- Check sample labelling against specimen acceptance criteria.
  - Samples which fail specimen acceptance criteria will be rejected

- Check details on referring form and indication for testing against the agreed clinical criteria:
  - Requests with incomplete information will be rejected and the sample disposed of, the referring laboratory will be contacted by email to inform them.

- If samples do not meet the testing criteria (see below) the referring laboratory will be informed by email. There will be an opportunity for the referring haematologist to discuss the case with laboratory or medical staff prior to disposal of the sample.

Referral forms for haemoglobinopathy genetic test requests, including a specific form for prenatal diagnosis referrals, can be found at the following link: https://mft.nhs.uk/nwglh

NHS E Test Directory 'R' codes

The laboratory will perform genotypic analysis according to the clinical details on the referral and the requested 'R' code. If there is any disparity between the indications, then the referrer will be consulted for clarification.

The NHS E National Genetic Test Directory can be found at the following link: https://www.england.nhs.uk/publication/national-genomic-test-directories/. For the haemoglobinopathy diagnostic service, the appropriate R codes are as follows:

R code	Test indication
R361	Haemoglobinopathy trait or carrier testing
R362	Carrier testing for sickle cell disease
R93	Thalassaemia and other haemoglobinopathies – Diagnostic testing
R94	Hb SS sickle cell anaemia
R92	Rare anaemia (to be used where the diagnosis is not likely to be thalassaemia)

Reporting

A genetic report, including phenotypic information where provided, will be sent from the Manchester Haemoglobinopathy Diagnostic Service with any necessary clinical interpretation.

The laboratory may be contacted for discussion of the haemoglobinopathy genetic results: email mft.genomics@nhs.net, or telephone 0161 276 6123 / 0161 701 4895.

For internal referrals, reports are reviewed against haemoglobinopathy phenotypic screens at the Haemoglobinopathy Multi-Disciplinary Team (MDT) meetings with input from the Clinical and Counselling services. For Clinical advice for internal referrals, please contact the haemoglobinopathy clinical team: email mft.haemoglobinopathy@nhs.net, or telephone Clinical Nurse Specialist 0161 701 4574 or Haemoglobinopathy Secretary 0161 701 2926.

For referrals external to MFT, complex cases may be reviewed at the NW GLH Haematology MDT prior to reporting of results. For Clinical advice, please consult your local Consultant Haematologist or Haemoglobinopathy Coordinating Centre (HCC).

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INDICATIONS FOR MOLECULAR TESTING

NB this list is not exhaustive. If in doubt about a referral, please contact the haemoglobinopathy clinical team on mft.haemoglobinopathy@nhs.net.

1. Antenatal or pre-conceptual counselling

Table of biological parental carrier state combinations taken from Appendix 3 of the NHS Sickle Cell and Thalassaemia Screening Programme Handbook for antenatal laboratories (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/656094/Antenatal_Laboratory_Handbook.pdf) accessed 26/02/2021. In addition to the carrier states identified, carriers of alpha zero thalassaemia confer a serious risk and prenatal diagnosis should be offered.

		Biological mother									
	Carrier of:	HbS	β thalassaemia	δβ thalassaemia	Hb Lepore	HbE	HbO^{Arab}	HbC	HbD^{Punjab}	HPFH	Not identified as a carrier
Biological father	HbS										
	β thalassaemia										
	δβ thalassaemia										
	Hb Lepore										
	HbE										
	HbO^{Arab}										
	HbC										
	HbD^{Punjab}										
	HPFH										
	Not identified as a carrier										

Key

- Serious risk - refer couple for counselling - prenatal diagnosis to be offered
- Less serious risk - refer couple for counselling - further investigation may be required
- Minimal risk

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National Screening Committee guidance:

Maternal carrier state	Paternal carrier state	Further studies by DNA analysis
No abnormalities detected	Partner testing not required	None required
Any abnormal Hb	No abnormality detected	None required
Hb S	Hb S or Hb C	None required until PND
Hb S	Hb O-Arab, D-Punjab, Lepore, β thalassaemia	Send bloods for mutation confirmation of paternal carrier
Hb S	HPFH	Send bloods for mutation confirmation of paternal carrier state; if confirmed, PND is not indicated
Hb C	Hb S	None required until PND
Hb D-Punjab	Hb S	Send bloods for mutation confirmation for suspected D-Punjab
Hb O-Arab	Hb S	Send bloods for mutation confirmation of Hb O-Arab
Hb Lepore	Hb S, E, O-Arab, Lepore, β thalassaemia	Send bloods for mutation confirmation of Hb Lepore or Hb O-Arab
Hb E*	β thalassaemia, Hb, Lepore,	Send bloods for mutation confirmation of β thalassaemia, Hb Lepore
β thalassaemia	Hb S, E, O-Arab, Lepore, β thalassaemia	Send bloods for mutation confirmation of β thalassaemia, Hb Lepore, Hb O- Arab
β thalassaemia*	Suspected α thalassaemia (MCH <25 pg)	Send bloods for mutation confirmation if of appropriate Mediterranean or SE Asian origin
suspected α^+ thalassaemia (MCH of 25–27pg)	Partner testing not required	None required
Suspected heterozygous α0 or homozygous α+ thalassaemia (MCH < 25pg) 1. Indian, Pakistani, African, North European, or Middle Eastern 2. South-East Asian, Eastern Mediterranean (Cyprus, Greece, Turkey, Sardinia), British** or unknown	Partner testing not required Test partner and if: • MCH < 25 pg and from high risk area • MCH ≥ 25 pg and/or low risk area	None required Send maternal and paternal bloods for mutation confirmation None required.

* = hidden risk of α thalassaemia ** = The NSC guidelines indicate that the partner need not be tested unless the patient is from a local high risk area (e.g. North-West England). PND = prenatal diagnosis

2. Carrier identification for genetic counselling purposes in non antenatal patients of appropriate age group.

- Diagnosis of unidentified Haemoglobin variants in pregnant women and/or partners (to link to variants identified in newborn screening programme)

3. Prenatal diagnosis

Prenatal diagnosis will be offered to couples at risk of having a child with any of the conditions that are listed below:
Hb SS, Hb SC, Hb SD^{Punjab}, Hb S/β thalassaemia ($β^o$, $β^+$, δβ thal, Lepore), Hb S/Hb O^{Arab}, Hb E/β thalassaemia, Hb Bart's hydrops fetalis ($α^o$ /$α^o$), β thalassaemia major

Parental samples are required to be tested by the laboratory, or a parental genetics report provided, prior to the PND procedure to establish the genotype to be identified in the fetal sample. A maternal blood sample must accompany the PND sample for maternal cell contamination testing, if performed at the NW GLH.

4. Newborn, Paediatric for genetic counselling and clinical management

- Genotypic investigation of B thalassaemia major/intermedia phenotype
- Investigation of Hb H disease (+ parents)
- Confirmation of Hb variant/ B thalassaemia, if not apparent from parental phenotypes.
- Unknown Hb variant analysis
- Sickle /HPFH

5. Adult haemoglobinopathy patients for genetic counselling and clinical management

- Genotypic investigation of B thalassaemia intermedia phenotype
- Investigation of abnormally raised Hb F levels (>5%)
- Confirmation of Hb variant/ thalassaemia if not apparent from phenotype

6. Investigation of possible alpha thalassaemia phenotype where clinically relevant (i.e. obviates need for further investigations)

These cases are extremely heterogeneous with many potential genetic defects. Testing is primarily indicated where it will impact on clinical management or where it is deemed important for genetic counselling. Family studies in such cases may be informative i.e. in compound heterozygous states and should be performed initially, if feasible.

- Thalassaemia intermedia phenotype (severe microcytic anaemia Hb > 2g/dL below normal range plus clinical features of haemolysis/splenomegaly, bone features, gallstones etc).
- Hb H disease
- Investigation of possible underlying alpha thalassaemia contributing to Anaemia of Chronic Disease when apparently iron replete

7. Investigation of unstable or high affinity haemoglobin

- Genotypic investigation of unstable of high affinity haemoglobins identified in phenotypic testing