Newborn Screening & Biochemical Genetics
West Midlands Laboratory Service for Inherited Metabolic Disorders
Handbook for Users

Contact numbers:
Duty BMS (results) 0121 333 9942
Duty biochemist (clinical queries, interpretation) 07795 828 617

Please check whether this is the current version of this handbook at:
https://bwc.nhs.uk/newborn-screening-and-biochemical-genetics
Department of Newborn Screening & Biochemical Genetics

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Service Scope

The service scope for the Department of Newborn Screening and Biochemical Genetics at Birmingham Children's Hospital NHS Foundation Trust (BCH) encompasses those defined by the UK NHS Blood Spot Screening Programme and by NHS England for Metabolic Disorders (Laboratory Services). It additionally includes highly specialised Biochemical and Molecular Genetic testing for inherited metabolic disorders, accessible to patients and clinicians worldwide.

Service Standards

The Department of Newborn Screening and Biochemical Genetics is accredited to Clinical Pathology Accreditation (CPA UK) standards (laboratory number 4023). Accreditation status can be checked at http://cpa-search.ukas.org/cpasearch/. The department is awaiting confirmation from UKAS of the laboratory’s accredited schedule to ISO15189:2012 standards (laboratory number 9948). Tests not in scope and therefore unaccredited and unaccredited tests referred to other laboratories are indicated with the symbol † in the repertoire tables. Once available, the scope will be published on the UKAS website.

Advisory Service

Duty biochemists for Newborn Screening and Biochemical Genetics are available for all queries concerning test selection and effective utilisation, clinical advice, result interpretation and urgent requests. Refer to the ‘Contacting the Laboratory’ section for contact details.

Services Provided

Newborn Screening

The West Midlands Newborn Screening Centre at BCH provides newborn bloodspot screening for congenital hypothyroidism, sickle cell disease, cystic fibrosis, phenylketonuria (including the investigation of biopterin defects), medium chain acyl CoA dehydrogenase deficiency, maple syrup urine disease, pyridoxine non-responsive homocystinuria, glutaric aciduria type 1, and isovaleric acidaemia. Please refer to the separate newborn screening handbook for further details.

Biochemical Genetics

The Biochemical Genetics laboratories provide biochemical, enzyme and DNA testing with result interpretation for the diagnosis, monitoring and clinical care of patients with inherited metabolic disorders, which are rare but serious conditions. The laboratory professionals are part of a wide multidisciplinary IMD team comprising clinical, nursing, dietetic, pharmacy and psychology staff. We have facilities for tissue banking and the culture and storage of skin fibroblasts, chorionic villus cells and amniotic fluid cells.

Antenatal Diagnosis

In liaison with the Regional Genetics Laboratory and Clinical Genetics Service we act as a centre for advice on antenatal testing options for inherited metabolic disorders and co-ordinate sample handling and the reporting of results. We attempt the audit of all antenatal diagnoses and record and report the results on an annual basis.
Service Commitment

The Department of Newborn Screening and Biochemical Genetics is committed to providing laboratory services of the highest quality within the resources available, and to continually evaluate and improve all aspects of the service. The department endeavours to:

- Provide accurate and timely results
- Provide advice on testing algorithms, sample requirements, result interpretation
- Meet the needs of our users
- Respond to feedback
- Improve the service on an ongoing basis
- Provide training for undergraduate and postgraduate Biomedical Scientists, Clinical Scientists and Clinicians

The laboratory is one of 17 stakeholders in the National Metabolic Biochemistry Network (http://www.metbio.net).

Patient Information

Testing is available to patients via appropriate healthcare professionals and is guided by clinical assessment. Under certain circumstances, the laboratory may undertake additional relevant testing dependent on the clinical information provided and the results of other analyses. Any additional testing performed will remain within the remit of the investigation of inherited metabolic disorders.

All patient information is held securely under the provisions of the UK Data Protection Act 1998. Results are communicated directly to the requesting healthcare professional, usually via the referring laboratory. Results may only be accessed by healthcare professionals directly involved in the care of the patient. The laboratory cannot currently provide results directly to patients; the relevant healthcare professional should be contacted for all result enquiries.

Relevant patient information can be requested from your healthcare professional and is provided at consultation. Useful websites include:

- NHS Newborn Screening Programme http://newbornbloodspot.screening.nhs.uk/public
- The National Information Centre for Metabolic Diseases http://www.climb.org.uk/
- Lab Tests Online (for non-IMD biochemistry tests) http://labtestsonline.org.uk/
Service Location & Availability

Service Hours

Normal Working Hours
The laboratory is open for the receipt and processing of routine samples and for result reporting and advice from 09:00-17:10h Monday to Friday (except Bank Holidays).

Out of Hours Service
Out-of-hours analytical services are available for plasma ammonia and plasma/CSF lactate as part of the Blood Sciences: Clinical Chemistry on-call service at BCH.

No other analytical service for IMD is routinely available out-of-hours but, in emergency, specific tests may be provided if clinically justified and if staff are available.

If analytical or advisory services are required out of hours please contact the on-call Consultant Biochemist in the first instance (via the BCH switchboard, Telephone No. 0121 333 9999).

Sending a Specimen
Information on sending specimens collected within Birmingham Children’s Hospital can be obtained from the Hospital Laboratory Handbook located on the Intranet.

Specimens collected at sites outside Birmingham Children’s Hospital should, where possible, be sent via the blood sciences/clinical chemistry department in the originating hospital. In some cases specimens for certain tests may require immediate transport by courier or taxi. Specific needs are listed in the specimen requirement section of the table in this handbook. If using a courier or taxi please request that the specimens are delivered to the Paediatric Laboratory Medicine Block entrance at Whittall Street (not to the main hospital post room).

Laboratory postal address
Pathology Reception
Dept of Newborn Screening & Biochemical Genetics
Paediatric Laboratory Medicine
Birmingham Children’s Hospital
Steelhouse Lane
Birmingham
B4 6NH

Delivery address for couriers
Pathology Reception
Dept of Newborn Screening & Biochemical Genetics
Paediatric Laboratory Medicine
Birmingham Children’s Hospital
Whittall Street
Birmingham
B4 6DH
Request forms and minimum data set

The request form must include a minimum of the following information:

1. Surname
2. Source of request i.e. originating hospital
3. Test requested
4. And two from
   a) Forename
   b) Date of birth
   c) Registration number

The following information is desirable:

- Forename
- Date of birth
- Sex
- Registration number
- NHS number
- Postcode (requirement for molecular genetic tests)
- Name of requesting consultant
- Sample type
- Date and time of specimen collection
- Referring laboratory specimen number
- Clinical details (including fasting status and current drug therapy)

Specimen labelling and minimum data set

The specimen must be labelled with the following information:

1. Surname
2. And two from
   a) Forename
   b) Date of birth
   c) Registration number
   d) Referring laboratory specimen number

Note: for samples in small cryotubes, due to space constraints two patient identifiers are acceptable: surname, and one from date of birth, registration number, referring laboratory specimen number.

The following information is desirable:

- Date and time of specimen collection
- Forename
- Date of birth
- Sex
- Sample type

Specimen rejection

We do not analyse incorrectly or inadequately labelled specimens and/or request forms (see above). Specimens that are inadequately labelled, in the incorrect anticoagulant or preservative, or are received too late after sampling will not usually be analysed and a report will be issued to this effect. If appropriate, unsatisfactory specimens will be stored with routine specimens for 3 months.
Specimen Handling

Consent
It is the responsibility of the requesting doctor to obtain consent for specimen collection and the tests requested. It is implicit in the receipt of the request form that consent has been obtained. We never request more sample than we need to but where there is material left over after laboratory testing, it may be used for other purposes such as quality assurance or audit, under the provisions of the Human Tissue Act 2004. Specific research is regulated separately by the ethics committee. Consent for the use of tissue requires that patients must be given the option to refuse permission for spare material to be used. When this occurs, each request to the laboratory must be clearly marked so that specimens are not used for other purposes.

There may be specific requirements for written consent for DNA tests sent to other countries, please contact the molecular genetics laboratory for further information.

Urgent Specimens
Urgent requests can often be dealt with more quickly if there is prior discussion with the team. If your request is urgent please contact the Duty Metabolic Biochemist (mobile via switchboard: 0121 333 9999).

High Risk Specimens
We do not routinely analyse high-risk specimens without prior discussion. Please contact the Duty Metabolic Biochemist before sending such specimens.

Specimen Storage
Plasma and urine specimens are stored frozen for 3 months prior to disposal. Tissue and DNA specimens are stored for 30 years.

Add-on Tests
To request additional tests on specimens already received by the laboratory, please telephone to discuss whether sufficient specimen is remaining and is suitable for analysis. For requests added subsequent to receipt of the specimen, turnaround times are from the date of test request. A specific request form for this purpose must be used. This is available at https://bwc.nhs.uk/download.cfm?doc=docm93ijim4n2211.docx.

Specimen Collection
Phlebotomy services are provided at Birmingham Children’s Hospital for inpatients and outpatients. Specimen collection requirements are provided in the relevant tables of this handbook. For specimens collected by patients and/or their parents/carers (e.g. urine or bloodspot/capillary blood samples), instruction leaflets and training are available and provided on request.
Specimen Testing

Testing Guidelines

Group Tests and Profiles
Some tests will detect a wide range of disorders that produce abnormalities in the particular group of analytes, e.g. amino acids, organic acids, acylcarnitines, mucopolysaccharides & very long chain fatty acids. This type of “Group Test” is often used as a first line test.

In other cases we have combined tests into a profile that is aimed at detecting disorders with a particular symptom or pattern of symptoms e.g. hepatosplenomegaly, hereditary optic atrophy.

A request for a urine “metabolic screen” will normally be interpreted by the laboratory as requiring urine amino acids, organic acids and “spot tests”. However if the clinical information supplied suggests other tests could be appropriate these may be added by the Duty Metabolic Biochemist.

Test Repertoire
The volume, specimen type and storage/transport requirements are detailed in the following tables. If the test you require is not included in our repertoire please contact us or visit the National Metabolic Biochemistry Website: http://www.metbio.net/metbioAssays.asp

Turnaround Times
Turnaround times quoted are the anticipated times between specimen receipt in our laboratory and reporting under normal operating conditions. The turnaround times of all tests are monitored. Results will normally be returned via the local laboratory at the requesting hospital. The times taken for the specimen to reach the laboratory and for the report to reach the requesting clinician are not included. When appropriate, abnormal results will be telephoned to the requesting physician.

Work Referred Away
The department regularly refers specimens to other specialist centres in order to provide a comprehensive diagnostic service. Most UK laboratories to which samples are referred are CPA or UKAS accredited. However, many of those from Europe and around the world are either not accredited or their accreditation status is unknown. The performance of referral laboratories is routinely monitored.

Where work has been done in other centres, this is made clear on our laboratory report. A list of referral laboratories is given in appendix D.

Test Cost
Within the West Midlands region the laboratory IMD services are provided by NHS England as part of specialist services commissioning. Services not covered by this arrangement are charged for on a cost per test basis. A price list is available on request.
## Metabolite tests

<table>
<thead>
<tr>
<th>Metabolite Test (Method)</th>
<th>Investigation</th>
<th>Specimen type/ volume</th>
<th>Specific needs</th>
<th>Storage</th>
<th>Transport</th>
<th>Turnaround time in working days (90th centile)</th>
<th>EQA scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-Dehydrocholesterol screen (Spectrophotometric)</td>
<td>Smith-Lemli-Opitz Syndrome</td>
<td>VP 0.5mL plasma or serum</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>15 days</td>
<td>ERNDIM</td>
<td></td>
</tr>
<tr>
<td>Acyl carnitines incl. free carnitine (FIA-MSMS)</td>
<td>Fatty acid oxidation defects Organic acid disorders</td>
<td>VB (Heparin 0.5mL) or BS VP (0.2mL)</td>
<td>Please send plasma AND blood spots</td>
<td>Room temperature Room temperature</td>
<td>15 days</td>
<td>ERNDIM CDC ERNDIM CDC</td>
<td></td>
</tr>
<tr>
<td>Amino Acids – Quantitative (AAA)</td>
<td>Amino acid disorders and urea cycle defects</td>
<td>VP (Heparin 0.5mL) CSF 0.5mL U (2mL)</td>
<td>Preferably send a fasting sample. Blood stained CSF is unsuitable for analysis.</td>
<td>Store frozen prior to shipment Send frozen if possible</td>
<td>15 days</td>
<td>ERNDIM UKNEQAS</td>
<td></td>
</tr>
<tr>
<td>Amino Acids (Qualitative) (HVE)</td>
<td>Renal transport disorders</td>
<td>U (2mL)</td>
<td>Store frozen prior to shipment Send frozen if possible</td>
<td>7 days</td>
<td>ERNDIM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pterins (HPLC)</td>
<td>Bipterin deficiency disorders</td>
<td>6x10mm BS (1x10mm extra BS if phenylalanine result is not provided)</td>
<td>Ideally collect when blood phenylalanine is increased</td>
<td>Store frozen prior to shipment.</td>
<td>Room temperature</td>
<td>15 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Carnitine – free (FIA – MSMS)</td>
<td>Carnitine status and transport disorders</td>
<td>U (0.5mL), VP (Heparin 0.2mL)</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>15 days</td>
<td>ERNDIM CDC</td>
<td></td>
</tr>
<tr>
<td>Cystine (AAA)</td>
<td>Cystinuria</td>
<td>U (0.5mL)</td>
<td>Store frozen prior to shipment. Send frozen if possible</td>
<td>15 days</td>
<td>ERNDIM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free Fatty Acids &amp; 3-Hydroxybutyrate (Enzymatic)</td>
<td>Hypoglycaemia</td>
<td>VP (Fluoride-Oxalate 0.5mL)</td>
<td>Please state fasting status.</td>
<td>Store frozen prior to shipment.</td>
<td>Room temperature</td>
<td>3 days</td>
<td>ERNDIM RANDOX</td>
</tr>
<tr>
<td>Galactose-1-Phosphate – Quantitative (Enzymatic)</td>
<td>Galactosaemia monitoring</td>
<td>Whole VB (Heparin 1mL)</td>
<td>The sample must be received within 24 hours of collection.</td>
<td>Room temperature Room temperature</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Glycosaminoglycans (Spectrophotometric and electrophoresis)</td>
<td>Mucopolysaccharides</td>
<td>U (5mL)</td>
<td>Store frozen prior to shipment Send frozen if possible</td>
<td>15 days (1D) 25 days (2D)</td>
<td>ERNDIM WILLINK MPS SCHEME</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolite Test (Method)</td>
<td>Investigation</td>
<td>Specimen type/ volume</td>
<td>Specific needs</td>
<td>Storage</td>
<td>Transport</td>
<td>Turnaround time in working days (90th centile)</td>
<td>EQA scheme</td>
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</tr>
<tr>
<td>Homocystine – free (HPLC)</td>
<td>Homocystinuria</td>
<td>VP (Heparin 0.5mL)</td>
<td>See sulphur-containing amino acids</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen</td>
<td>15 days</td>
<td>ERNDIM</td>
</tr>
<tr>
<td>Homocysteine – total (HPLC-MSMS)</td>
<td>Homocystinuria</td>
<td>VP 0.2mL (or BS for monitoring known patients)</td>
<td>Separate within 30 minutes of collection</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>7 days - DBS 10 days – plasma</td>
<td>ERNDIM</td>
</tr>
<tr>
<td>Methylmalonic acid – Quantitative (GCMS)</td>
<td>Methylmalonic aciduria</td>
<td>VP (Heparin 1mL)</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>ERNDIM (plasma only)</td>
<td></td>
</tr>
<tr>
<td>Nitisinone – NTBC (HPLC-MSMS)</td>
<td>Tyrosinaemia type-1 (therapeutic drug monitoring)</td>
<td>VS or VP (Heparin 1mL)</td>
<td>Collect specimen pre-dose</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Oligosaccharides (TLC)</td>
<td>Oligosaccharidoses</td>
<td>U (1mL)</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Organic Acid Analysis (GCMS)</td>
<td>Organic acid disorders and urea cycle defects</td>
<td>U (5mL)</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>10 days</td>
<td>ERNDIM</td>
<td></td>
</tr>
<tr>
<td>Orotic Acid – Quantitative (GCMS)</td>
<td>Urea cycle defects</td>
<td>U (5mL)</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>ERNDIM</td>
<td></td>
</tr>
<tr>
<td>Oxalate (Enzymatic)</td>
<td>Renal stones – Oxalosis</td>
<td>VP (EDTA 1mL)</td>
<td>Plasma must be separated within 30 minutes of venepuncture</td>
<td>Store frozen prior to shipment</td>
<td>Must be sent frozen</td>
<td>15 days</td>
<td>ERNDIM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U (5mL)</td>
<td>Acidify urine to pH&lt;2 within 30 mins of voiding, or collect 24h urine into acid containing bottle</td>
<td></td>
<td>Send frozen if possible</td>
<td></td>
<td>RANDOX</td>
</tr>
<tr>
<td>Phenylalanine &amp; tyrosine (FIA-MSMS)</td>
<td>Phenylketonuria &amp; tyrosinaemia (monitoring)</td>
<td>2x10mm BS</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>3 days</td>
<td>UKNEQAS CDC</td>
<td></td>
</tr>
<tr>
<td>Phosphoethanolamine (AAA)</td>
<td>Hypophosphatasia</td>
<td>U (5mL)</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>ERNDIM</td>
<td></td>
</tr>
<tr>
<td>Metabolite Test (Method)</td>
<td>Investigation</td>
<td>Specimen type/ volume</td>
<td>Specific needs</td>
<td>Storage</td>
<td>Transport</td>
<td>Turnaround time in working days (90th centile)</td>
<td>EQA scheme</td>
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</tr>
<tr>
<td>Phytanic &amp; Pristanic acids (GCMS)</td>
<td>Peroxisomal disorders</td>
<td>VP (Heparin, Fluoride-Oxalate or EDTA 1mL)</td>
<td></td>
<td>Store frozen prior to shipment</td>
<td>Send at room temperature</td>
<td>15 days</td>
<td>ERNDIM</td>
</tr>
<tr>
<td>†Reducing substances (Colourimetric)</td>
<td>Renal reabsorption. GI absorption/ transport/ metabolism</td>
<td>U (5mL)</td>
<td>Faeces (liquid)</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>3 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Succinylacetone (HPLC-MSMS)</td>
<td>Tyrosinaemia type-1</td>
<td>VS or VP (Heparin 1mL)</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>†Sugar chromatography of mono &amp; disaccharides (TLC)</td>
<td>Renal reabsorption. GI absorption/ transport/ metabolism</td>
<td>U (5mL)</td>
<td>Faeces (liquid)</td>
<td>Only routinely analysed if reducing substances positive</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
</tr>
<tr>
<td>Sulphur-containing Amino Acids: Quantitative free cystine, free homocystine and methionine (AAA)</td>
<td>Homocystinuria</td>
<td>VP (Heparin 0.5mL)</td>
<td>Separate within 30 minutes of collection and deproteinise immediately (Deproteinising solution available to referring hospitals on request)</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen</td>
<td>15 days</td>
<td>ERNDIM</td>
</tr>
<tr>
<td>Sulphocysteine – also request free and total homocyst(e)ine (AAA)</td>
<td>Sulphite oxidase/ molybdenum cofactor deficiency</td>
<td>VP (Heparin 0.5mL)</td>
<td>See sulphur-containing amino acids</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen</td>
<td>15 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Transferrin Isoforms (HPLC)</td>
<td>Congenital Disorders of Glycosylation</td>
<td>VS 0.5 mL</td>
<td>None</td>
<td>Room temperature</td>
<td>25 days</td>
<td>ERNDIM</td>
<td></td>
</tr>
<tr>
<td>Very long chain fatty acids (GCMS)</td>
<td>Peroxisomal disorders</td>
<td>VP (Heparin, Fluoride-Oxalate or EDTA 2mL)</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>15 days</td>
<td>ERNDIM</td>
<td></td>
</tr>
<tr>
<td>Metabolite Test (Method)</td>
<td>Investigation</td>
<td>Specimen type/ volume</td>
<td>Specific needs</td>
<td>Storage</td>
<td>Transport</td>
<td>Turnaround time in working days (90th centile)</td>
<td>EQA scheme</td>
</tr>
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</tr>
<tr>
<td>White Cell Cystine (AAA)</td>
<td>Cystinosis</td>
<td>VB (Heparin 5mL –for monitoring, 10mL for diagnosis)</td>
<td>Prior arrangement essential</td>
<td>Do not freeze</td>
<td>Send whole blood to arrive before 1pm on the day of sampling</td>
<td>15 days</td>
<td>ERNDIM</td>
</tr>
</tbody>
</table>

BS = bloodspot, U = urine, VB = venous blood, VS = venous serum, VP = venous plasma (anticoagulant stated). AAA = Amino Acid Analyser, HPLC = High Pressure Liquid Chromatography, FIA = Flow injection analysis, MSMS = Tandem Mass Spectrometry, GCMS = Gas Chromatography Mass Spectrometry, TLC = thin layer chromatography, N/A = no EQA scheme available. †test not included in UKAS accreditation scope.

For tests not performed by this laboratory (i.e. those tests not listed in the table), please contact us to discuss the most appropriate referral laboratory for testing and relevant specimen handling requirements.
Lysosomal Enzyme Tests

Lysosomal Enzyme Assays
Assays are typically performed on leucocytes isolated from whole blood collected into EDTA. All samples should be received in our Department within 24 hours of collection to ensure an optimum yield of cells. Samples must arrive Mon-Thu or by 10am Friday at the latest, i.e. collect Mon-Thu if to be sent overnight or Mon-Wed if to come via standard transport from another hospital. Please do not use first or second-class post. Samples can be stored overnight at +4°C but DO NOT FREEZE OR SEPARATE. The volume of blood required varies according to the number and type of tests requested. For these reasons it is important to contact the laboratory prior to taking the sample. Some enzymes can be measured on plasma or blood spots as an initial screen but any abnormal result should be confirmed on leucocytes isolated from whole blood. Unless pre-agreed we will test plasma or bloodspots in the first instance.

Group Tests of Lysosomal Enzymes
Gangliosidosis Profile (5mL EDTA)
Leucocyte β-galactosidase (GM1 Gangliosidosis & Galactosialidosis)
Leucocyte total hexosaminidase (Sandhoff disease)
Leucocyte hexosaminidase A (Tay-Sachs disease).

Hepatosplenomegaly Profile (5mL EDTA)
Leucocyte sphingomyelinase (Niemann-Pick disease type A & B)
Leucocyte β-glucosidase (Gauches disease)
Leucocyte acid esterase (Wolman disease & Cholesteryl Ester Storage disease)
Plasma chitotriosidase (Non specific screen for some lysosomal disorders such as Gaucher disease and Niemann-Pick disease type C – screening test only).

Dysmorphic Profile (10mL EDTA)
(See http://www.metbio.net/metbioGuidelines.asp for guidelines)
Plasma I-cell Screen (Mucolipidosis II & III)
Plasma aspartylglucosaminidase (Aspartylglucosaminuria)
Leucocyte arylsulphatase A (Multiple Sulphatase Deficiency)
Plasma /Leucocyte β-glucuronidase (MPS VII)
Leucocyte β-galactosidase (GM1-gangliosidosis & galactosialidosis)
Plasma/ Leucocyte α- & β-mannosidase (α- & β-mannosidosis)
Plasma/ Leucocyte α-fucosidase (α-fucosidosis)

Leucodystrophy Profile (10mL EDTA)
Leucocyte arylsulphatase A (Metachromatic leucodystrophy)
Leucocyte β-galactocerebrosidase (Krabbe leucodystrophy).

Batten Disease Profile (10mL EDTA)
Leucocyte palmitoyl protein thioesterase 1 (CLN1)
Leucocyte tripeptidyl peptidase 1 (CLN2)

Foetal/Neonatal Hydrops Profile (10mL EDTA)
(See http://www.metbio.net/metbioGuidelines.asp for guidelines).
Leucocyte β-glucosidase (Gaucher Disease)
Plasma/ Leucocyte β-glucuronidase (MPS VII)
Leucocyte β-galactosidase (GM1 gangliosidosis & galactosialidosis),
Leucocyte sphingomyelinase (Niemann-Pick A & B)
Leucocyte acid esterase (Wolman disease & Cholesteryl Ester Storage disease)
Leucocyte arylsulphatase A (Metachromatic leucodystrophy)
Plasma chitotriosidase (Non specific screen for some lysosomal disorders such as Gaucher disease and Niemann-Pick disease type C – screening test only).
### Enzyme tests in blood (whole blood, bloodspots, red blood cells, leucocytes, plasma and serum)

<table>
<thead>
<tr>
<th>Blood Enzyme Test</th>
<th>Investigation</th>
<th>Specimen type/ volume</th>
<th>Specific needs</th>
<th>Storage</th>
<th>Transport</th>
<th>Turnaround time in working days (90th centile)</th>
<th>EQA scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Esterase / Lysosomal Acid Lipase (LAL)</td>
<td>Wolman/Cholesteryl Ester Storage Disease/Lysosomal Acid Lipase deficiency</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td></td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBS (EDTA)*</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>α-N-Acetylgalactosaminidase</td>
<td>Schindler Disease</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td></td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBS (EDTA)*</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>15 days</td>
<td>N/A</td>
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<tr>
<td>α-Galactosidase A</td>
<td>Fabry Disease Males only</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td></td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBS (EDTA)*</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>α-Fucosidase</td>
<td>Fucosidosis</td>
<td>VP/VS Heparin, EDTA, Clotted 0.2mL</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td></td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>N/A</td>
</tr>
<tr>
<td>α-Mannosidase</td>
<td>α-Mannosidosis</td>
<td>VP/VS Heparin, EDTA, Clotted 0.2mL</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td></td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
</tr>
<tr>
<td>α-Glucosidase (Acid Maltase)</td>
<td>GSD II, Pompe Disease</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td></td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBS (EDTA)*</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td>15 days</td>
<td>N/A</td>
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</tr>
<tr>
<td>Arylsulphatase A</td>
<td>Metachromatic Leucodystrophy</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td></td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
</tr>
<tr>
<td>Blood Enzyme Test</td>
<td>Investigation</td>
<td>Specimen type/ volume</td>
<td>Specific needs</td>
<td>Storage</td>
<td>Transport</td>
<td>Turnaround time in working days (90th centile)</td>
<td>EQA scheme</td>
</tr>
<tr>
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<tr>
<td>Aspartylglucosaminidase</td>
<td>Aspartylglucosaminuria</td>
<td>VP/VS Heparin, EDTA, Clotted 0.2mL</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>β-Galactocerebrosidase (Galactosylceramidase)</td>
<td>Krabbe Leucodystrophy</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
<td></td>
</tr>
<tr>
<td>β-Galactosidase</td>
<td>GM1 Gangliosidosis</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBS (EDTA)*</td>
<td>Store frozen prior to shipment</td>
<td>Room temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Glucosidase (Glucocerebrosidase)</td>
<td>Gaucher Disease</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
<td></td>
</tr>
<tr>
<td>β-Glucuronidase</td>
<td>Sly Disease, MPS VII</td>
<td>VP/VS Heparin, EDTA, Clotted 0.2mL</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>β-Mannosidase</td>
<td>β-Mannosidosis</td>
<td>VP/VS Heparin, EDTA, Clotted 0.2mL</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Biotinidase</td>
<td>Biotinidase deficiency</td>
<td>VP (Heparin 1mL)</td>
<td>Store frozen prior to shipment</td>
<td>Courier or taxi</td>
<td>10 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Chitotriosidase</td>
<td>Screen for lysosomal disorders</td>
<td>VP/VS Heparin, EDTA, Clotted 0.2mL</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>10 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine Reductase (DHPR)</td>
<td>DHPR deficiency</td>
<td>2x10mm BS</td>
<td>A blood transfusion within 6 weeks prior to sampling may invalidate results</td>
<td>Store frozen prior to shipment. Room temperature</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Blood Enzyme Test</td>
<td>Investigation</td>
<td>Specimen type/ volume</td>
<td>Specific needs</td>
<td>Storage</td>
<td>Transport</td>
<td>Turnaround time in working days (90th centile)</td>
<td>EQA scheme</td>
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</tr>
<tr>
<td>Fumarylacetoacetate Lyase</td>
<td>Tyrosinaemia Type 1</td>
<td>VB (EDTA 10mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>Please enquire</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Fructose 1,6 Bisphosphatase</td>
<td>Fructose 1,6 Bisphosphatase deficiency</td>
<td>VB (EDTA 10mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>Please enquire</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Galactose-1-phosphate uridytransferase screen</td>
<td>Galactosaemia</td>
<td>VB (Heparin 0.5mL)</td>
<td>A blood transfusion within 6 weeks prior to sampling may invalidate results</td>
<td>Do not freeze</td>
<td>Store frozen prior to shipment.</td>
<td>Room temperature</td>
<td>CDC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2X10mm BS or packed red cells</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Glucose-6-Phosphate Dehydrogenase</td>
<td>G6PD def</td>
<td>VB (1 mL preferably Heparin but EDTA is acceptable)</td>
<td>A blood transfusion within 6 weeks of sampling may invalidate results</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>10 days</td>
<td>UKNEQASH</td>
</tr>
<tr>
<td>Hexosaminidase A</td>
<td>Tay-Sachs Disease</td>
<td>VP/VS Heparin, EDTA, Clotted 0.2mL</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>See below</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
<td></td>
</tr>
<tr>
<td>Hexosaminidase (Total)</td>
<td>Sandhoff Disease</td>
<td>VP/VS Heparin, EDTA, Clotted 0.2mL</td>
<td>Store frozen prior to shipment</td>
<td>Send frozen if possible</td>
<td>15 days</td>
<td>See below</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
<td></td>
</tr>
<tr>
<td>Palmitoyl Protein Thioesterase 1</td>
<td>CLN1 (Batten)</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Porphobilinogen (PBG) synthase inhibition</td>
<td></td>
<td>No longer available – replaced by succinyl acetone (VP/BS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Enzyme Test</td>
<td>Investigation</td>
<td>Specimen type/ volume</td>
<td>Specific needs</td>
<td>Storage</td>
<td>Transport</td>
<td>Turnaround time in working days (90th centile)</td>
<td>EQA scheme</td>
</tr>
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<td>----------------------------</td>
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</tr>
<tr>
<td><strong>Sphingomyelinase</strong></td>
<td>Niemann-Pick disease types A &amp; B</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>ERNDIM~</td>
<td></td>
</tr>
<tr>
<td><strong>Steroid Sulphatase</strong></td>
<td>X-linked ichthyosis, Multiple sulphatase deficiency</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Tripeptidyl Peptidase 1</strong></td>
<td>CLN2 (Batten)</td>
<td>VB (EDTA 5mL)</td>
<td>Do not freeze</td>
<td>For receipt within 24h of collection</td>
<td>15 days</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

BS = bloodspot, U = urine, VB = venous blood, VS = venous serum, VP = venous plasma (anticoagulant stated). *abnormal results require confirmation in leucocytes. ~ERNDIM scheme is performed on fibroblasts and the range of enzymes tested varies from year to year. N/A = no scheme available.
Tissue and Fibroblast Tests

Cell Culture
Skin biopsies should be collected in a sterile manner (See Appendix) and transported unfrozen in tissue culture medium guaranteed to reach us within 24 hours of being taken. A guideline for sampling and storage is available. Skin biopsies will be cultured (in most cases) and the cultured fibroblasts grown will be cryopreserved in liquid nitrogen and stored for 30 years (unless earlier disposal is specifically requested). Similarly all cultured chorionic villus cells and cultured amniotic fluid cells will be cryopreserved and stored for 30 years.

Tissue and Fibroblast Enzyme Tests

<table>
<thead>
<tr>
<th>Tissue Enzyme Test</th>
<th>Investigation</th>
<th>Specimen type/ volume</th>
<th>Specific needs</th>
<th>Storage</th>
<th>Transport</th>
<th>Turnaround time</th>
<th>EQA scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>†Citrulline Incorporation</td>
<td>Citrullinaemia &amp; Argininosuccinic Aciduria</td>
<td>SB (Culture)</td>
<td>Sterile collection</td>
<td>Culture medium Do not freeze</td>
<td>Room temperature</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td>†Butyrate $^{14}$CO$_2$ Release</td>
<td>Short Chain Fatty Acid Oxidation Defects</td>
<td>SB (Culture)</td>
<td>Sterile collection</td>
<td>Culture medium Do not freeze</td>
<td>Room temperature</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td>Duodenal Disaccharidases</td>
<td>Inherited Lactase/Sucrase Isomaltase Deficiency</td>
<td>Duodenal Tissue &gt;10mg</td>
<td>Freeze immediately</td>
<td>Coldest freezer available</td>
<td>Courier or taxi on dry ice</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td>Fructose 1,6 Bisphosphatase</td>
<td>Fructose Bisphosphatase Deficiency</td>
<td>Liver (Two Trucut Wedges) &gt;10 mg</td>
<td>Freeze immediately</td>
<td>Coldest freezer available</td>
<td>Courier or taxi on dry ice</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td>Fumarlycetoacetate Lyase</td>
<td>Tyrosinaemia Type 1</td>
<td>SB (Culture)</td>
<td>Sterile collection</td>
<td>Culture medium Do not freeze</td>
<td>Room temperature</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Glycine Cleavage Enzyme System</td>
<td>Non-Ketotic Hyperglycinemia</td>
<td>Liver (Two Trucut Wedges) &gt;10 mg</td>
<td>Freeze immediately</td>
<td>Coldest freezer available</td>
<td>Courier or taxi on dry ice</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td>†Isovaleric Acid Incorporation</td>
<td>Isovaleric Acidemia &amp; Hydroxymethylglutaric Aciduria</td>
<td>SB (Culture)</td>
<td>Sterile collection</td>
<td>Culture medium Do not freeze</td>
<td>Room temperature</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td>†Leucine $^{14}$CO$_2$ Release</td>
<td>Maple Syrup Urine Disease</td>
<td>SB (Culture)</td>
<td>Sterile collection</td>
<td>Culture medium Do not freeze</td>
<td>Room temperature</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td>Tissue Enzyme Test</td>
<td>Investigation</td>
<td>Specimen type/ volume</td>
<td>Specific needs</td>
<td>Storage</td>
<td>Transport</td>
<td>Turnaround time</td>
<td>EQA scheme</td>
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</tr>
<tr>
<td>Myristate/Oleate Fatty Acid Oxidation Flux Assays (³H Release)</td>
<td>Medium &amp; Long Chain Fatty acid oxidation defects</td>
<td>SB (Culture)</td>
<td>Sterile collection</td>
<td>Culture medium</td>
<td>Room temperature</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Do not freeze</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†Ornithine Incorporation</td>
<td>Hyperornithinaemia with Gyrate Atrophy of the Retina (HOGA) &amp; Hyperammonaemia with Hyperornithinaemia &amp; Homocitrullinuria (HHH)</td>
<td>SB (Culture)</td>
<td>Sterile collection</td>
<td>Culture medium</td>
<td>Room temperature</td>
<td>Please enquire</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Do not freeze</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SB = skin biopsy. N/A = no scheme available. †test not included in UKAS accreditation scope
DNA Analysis

Sample requirement: - 3ml whole blood in EDTA sent at room temperature as whole blood, or extracted DNA. The specimen can be sent by first class post. Analysis can also be performed on other material e.g. muscle, saliva, urine – please contact the laboratory concerning specimen requirements.

Mitochondrial DNA Encoded Mutations

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Mutation(s)</th>
<th>Method</th>
<th>Turnaround time in working days (90th centile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke like Episodes)</td>
<td>Mitochondrial DNA (TRNL1)</td>
<td>m.3243A&gt;G</td>
<td>PCR/RFLP and ARMS analysis</td>
<td>20</td>
</tr>
<tr>
<td>MERRF (Myoclonic Epilepsy with Ragged Red Fibres)</td>
<td>Mitochondrial DNA (TRNK)</td>
<td>m.8344A&gt;G</td>
<td>PCR/RFLP</td>
<td>20</td>
</tr>
<tr>
<td>NARP (Neurogenic Muscle Weakness, Ataxia &amp; Retinitis Pigmentosa)</td>
<td>Mitochondrial DNA (ATP6)</td>
<td>m.8993 T&gt;G/C</td>
<td>PCR/RFLP</td>
<td>20</td>
</tr>
<tr>
<td>DEAF (Maternally Inherited Antibiotic Induced Deafness)</td>
<td>Mitochondrial DNA (RNR1)</td>
<td>m.1555A&gt;G</td>
<td>PCR/RFLP</td>
<td>20</td>
</tr>
<tr>
<td>LHON (Leber Hereditary Optic Neuropathy)</td>
<td>Mitochondrial DNA (ND4)</td>
<td>m.11778G&gt;A</td>
<td>PCR/RFLP</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial DNA (ND1)</td>
<td>m.3460G&gt;A</td>
<td>PCR/RFLP</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial DNA (ND6)</td>
<td>m.14484T&gt;C</td>
<td>PCR/RFLP</td>
<td>20</td>
</tr>
<tr>
<td>Kearns-Sayre Syndrome, CPEO (Chronic Progressive External Ophthalmoplegia), Pearson Syndrome</td>
<td>Mitochondrial DNA</td>
<td>Rearrangements</td>
<td>Long Range PCR</td>
<td>20</td>
</tr>
</tbody>
</table>

Group Tests of Mitochondrial DNA Mutations

<table>
<thead>
<tr>
<th>Leber Hereditary Optic Atrophy</th>
<th>Mitochondrial DNA Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHON m.11778G&gt;A</td>
<td>MELAS m.3243A&gt;G</td>
</tr>
<tr>
<td>LHON m.3460G&gt;A</td>
<td>MERRF m.8344A&gt;G</td>
</tr>
<tr>
<td>LHON m.14484T&gt;C</td>
<td>NARP m.8993T&gt;G or C</td>
</tr>
<tr>
<td>Disorder</td>
<td>Gene</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD)</td>
<td>Medium Chain Acyl CoA Dehydrogenase (ACADM)</td>
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<tr>
<td>Long Chain Acyl CoA Dehydrogenase Deficiency (LCHADD)</td>
<td>Mitochondrial Trifunctional Protein Alpha Subunit (HADHA)</td>
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<td>Galactosaemia (Classical)</td>
<td>Galactose-1-Phosphate Uridyl Transferase (GALT)</td>
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<tr>
<td>McArdle Disease (Glycogen storage disease type V)</td>
<td>Muscle Glycogen Phosphorylase (PYGM)</td>
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<tr>
<td>†Myoadenylate Deaminase Deficiency (adenosine monophosphate deaminase 1)</td>
<td>Myoadenylate Deaminase (AMPD1)</td>
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<tr>
<td>Carnitine Palmitoyl Transferase II Deficiency</td>
<td>Carnitine Palmitoyl Transferase 2 (CPT2)</td>
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<td>Pseudodeficiency State for Arylsulphatase A</td>
<td>Arylsulphatase A (ARSA)</td>
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<tr>
<td>Tyrosinaemia Type I</td>
<td>Fumarylacetoacetate hydrolase (FAH)</td>
</tr>
<tr>
<td>†Glycogen Storage Disease Type I Non-A</td>
<td>Glucose-6-Phosphate Transporter (SLC37A4)</td>
</tr>
<tr>
<td>†Glycogen Storage Disease Type IA</td>
<td>Glucose-6-phosphatase (G6PC)</td>
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<td>Menkes Disease</td>
<td>ATP7A</td>
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<td>Non-Ketotic Hyperglycinaemia (NKH) Glycine encephalopathy (GCE)</td>
<td>Glycine decarboxylase (GLDC) P Protein</td>
</tr>
<tr>
<td></td>
<td>Amino methyl-transferase (AMT) Glycine cleavage system T Protein (GCST)</td>
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</tbody>
</table>
Isovaleric aciduria
Isovaleryl CoA dehydrogenase (IVD) c.941C>T p.(Ala314Val) PCR/sequencing 10

†Juvenile neuronal ceroid lipofuscinosis (JNCL) Batten disease type 3
CLN3 1.02kb deletion Deletion breakpoint PCR 20

† - 10d for testing for known mutations in family members; 3d for prenatal diagnosis †test not included in UKAS accreditation scope

EQA schemes
Specific schemes are not available for the majority of the genes investigated in our repertoire, however the schemes participated in cover the range of techniques used within the laboratory. The molecular biology laboratory participates in the following EQA schemes:

- UK NEQAS for Molecular Genetics mitochondrial diseases
- UK NEQAS for Molecular Genetics MCADD
- UK NEQAS for Molecular Genetics MCADD in blood spots
- UK NEQAS for Molecular Genetics cystic fibrosis in blood spots
- CDC Newborn Screening Quality Assurance Program cystic fibrosis mutation detection
- UK NEQAS for Molecular Genetics Pathogenicity of sequence variants interpretation only
Result Interpretation

Key factors affecting test performance
Many factors can affect biochemical results; diurnal rhythm, exercise, fasting status, drug therapy, method of specimen collection (e.g. venous or capillary), haemolysis and biological variation. Some drugs interfere with certain analyses therefore it is helpful to provide a list of current therapy on the request form accompanying the specimen. If specimens are not stored and transported as indicated in the tables below, results of some analytes may be affected. If urine specimens show signs of deterioration a repeat specimen is usually requested because diagnostic abnormalities may not be apparent.

Interpretation of Results
For qualitative tests, a written explanation of the observed result(s) is provided on the report. For quantitative tests that produce a numerical result, the appropriate biological reference interval or clinical decision value is provided on the final report to guide interpretation. Reference intervals are not provided in this handbook because: the majority are age and/or sex related; their significance may be dependent on the results of other investigations; they may not be appropriate under certain clinical scenarios; they may therefore be misleading or misinterpreted. Reference intervals and advice on result interpretation are available from the duty biochemist.

Contacting the Laboratory

<table>
<thead>
<tr>
<th>Telephone</th>
<th>Duty Metabolic Biochemist (clinical queries)</th>
<th>Duty Biomedical Scientist (IMD results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile: 07795 828617</td>
<td></td>
<td>0121 333 9942</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Molecular Genetics</th>
<th>Enzymes and Tissue Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>0121 333 9877</td>
<td>0121 333 9902</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fax Number</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>0121 333 9911</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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</table>

<table>
<thead>
<tr>
<th>Email</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Molecular genetics lab: <a href="mailto:bwc.biochemicalgenetics@nhs.net">bwc.biochemicalgenetics@nhs.net</a></td>
<td></td>
</tr>
<tr>
<td>IMD lab: <a href="mailto:bwc.imdlab@nhs.net">bwc.imdlab@nhs.net</a></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postal address</th>
<th>Dept of Newborn Screening &amp; Biochemical Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric Laboratory Medicine</td>
<td>Birmingham Children’s Hospital Steelhouse Lane Birmingham B4 6NH</td>
</tr>
</tbody>
</table>

To make a complaint
In the event that we do not meet your expectations, we would like to know so that we can improve our future service provision. Please contact us either directly or via the hospital complaints service, and provide as much information as possible surrounding your concerns. We endeavour to reply to and resolve all complaints received in a timely fashion.
### Staff Contact Details

<table>
<thead>
<tr>
<th>Scientific Staff</th>
<th></th>
</tr>
</thead>
</table>
| **Mrs Mary Anne Preece**  
Consultant Biochemist & Head of Department  
Director of Newborn Screening and Laboratory IMD  
0121 333 9940  
maryanne.preece@nhs.net |  |
| **Dr Adam Gerrard**  
Principal Clinical Scientist  
Metabolites  
0121 333 9903  
adam.gerrard@nhs.net |  |
| **Dr Pippa Goddard**  
Consultant Biochemist  
Newborn screening, Pterins  
0121 333 9927  
philippa.goddard@nhs.net |  |
| **Ms Carol Hardy**  
Principal Molecular Geneticist  
Molecular Genetics  
0121 333 9877  
carolhardy2@nhs.net |  |
| **Mr Russell Denmeade**  
Lead Biomedical Scientist  
NSBG  
0121 333 9938  
russell.denmeade@nhs.net |  |
| **Ms Sarah Dowden**  
Principal Clinical Scientist  
0121 333 9941  
sarah.dowden@nhs.net |  |
| **Dr Tim Hutchin**  
Principal Clinical Scientist  
Storage Disorders & Tissue Enzymes  
0121 333 9902  
timhutchin@nhs.net |  |
| **Mrs Jessica Schroeder**  
Principal Clinical Scientist  
0121 333 9941  
jessica.schroeder@nhs.net |  |
| **Mr Graeme Elliott**  
Senior Molecular Geneticist  
0121 333 9877  
graeme.elliott@nhs.net |  |
| **Mrs Louise Allen, Mrs Lisa Brown, Ms Joanna Mason**  
Senior Biomedical Scientists, IMD  
0121 333 9942  
louise.allen5@nhs.net, lisa.brown13@nhs.net, joanna.mason1@nhs.net |  |
| **Dr Greg Toulson**  
Senior Clinical Scientist  
0121 333 9948  
greg.toulson@nhs.net |  |
| **Mrs Yvette Taylor**  
Senior Biomedical Scientist  
0121 333 9877  
yvette.taylor2@nhs.net |  |
| **Dr Suresh Vijay**  
suresh.vijay1@nhs.net |  |
| **Dr Saikat Santra (clinical lead)**  
s.santra@nhs.net |  |
| **Dr Julian Raiman**  
Julian.Raiman@nhs.net |  |
| **Dr Srividya Sreekantam (locum)**  
s.sreekantam1@nhs.net |  |
| **Dr Tarek Hiwot**  
tarekegn.hiwot@uhb.nhs.uk |  |
| **Dr Charlotte Dawson**  
charlotte.dawson@uhb.nhs.uk |  |

### Consultant Metabolic Paediatricians

| Birmingham Children’s Hospital  
0121 333 9908 | University Hospital Birmingham  
0121 627 1627 ext 51592 |
Appendix A: Guidelines on Technique of Skin Biopsy for Inherited Metabolic Disorders

When a sample of the skin is required for fibroblast culture for investigations for inherited metabolic disorders, a minor surgical procedure is undertaken in order to obtain a suitable biopsy sample.\(^1\) Skin biopsy taken via a punch device as detailed below is the preferred method; other methods include a shave biopsy or surgical excision. Under normal circumstances biopsies should not be taken without prior arrangement with the laboratory: Department of Newborn Screening and Biochemical Genetics, Birmingham Children's Hospital, Tel No. 0121 333 9942.

NOTE THAT A SKIN BIOPSY IS OFTEN COLLECTED FOR HISTOLOGICAL ANALYSIS AND THAT THE SAMPLE HANDLING FOR THIS IS DIFFERENT. Please contact your local histopathology department for advice.

This procedure may be performed on the Ward, outpatients or in the operating theatre, by a trained Health care professional (any training should include the practical procedure, psychological aspects).\(^2,3,4\) A local anaesthetic is used when carrying out the procedure, rarely; oral sedation may also be required.\(^5,6\) An aseptic non-touch technique should be employed throughout the procedure.\(^1,4,7,10\) Consent must be obtained following BCH policy.\(^8,9,11\) Ensure the Skin Biopsy Consent form is signed and filed in the patient notes detailing consent to the procedure, analysis and storage of cells and asking whether patient/parents agree to subsequent storage of cells for quality control, comparison purposes and/or research. Information given should include the rationale for the biopsy, procedure and risks involved, side effects such as healing and scarring and a time line to expected results.\(^4,12,13\) The possibility of contamination or poor growth\(^1\) and repeat biopsy should be discussed where possible. Should a repeat biopsy be required referral to the play specialists may be appropriate.

**Equipment**
- Plastic apron
- Sterile gloves
- Sterile dressing pack
- 25 Fg needle (orange)
- 23 Fg needle (blue)
- 2 ml syringe
- A labelled skin biopsy cryotube (Obtainable from IMD laboratory Ext 9942)
- 4mm Punch Device
- Lignocaine 1%
- Local anaesthetic and appropriate covering/dressing (Ametop gel or Emla cream)
- Normal saline sachet
- ChloraPrep Sepp (Chlorhexidine 2% in 70% alcohol)
- Steristrips
- Small Mepore dressing.
- Sterile scissors or scalpel blade

**Sample requirements**
A skin biopsy should be collected using a 4mm punch; smaller diameter punches may give insufficient sample for reliable culture. The inner sides of the forearm or posterior aspect just above the elbow are the preferred sites.\(^1\)
Appendix A cont’d: Guidelines on Technique of Skin Biopsy for Inherited Metabolic Disorders

Technique

- Apply local anaesthetic cream or gel to the biopsy site (following consultation with the family re allergies) and cover with appropriate dressing. Leave for a minimum of 30 minutes. ¹,⁵,⁶,¹³
- Position the child, continue to maintain the dignity of the child whilst placing them in a comfortable position with the potential biopsy area exposed. Small children/infants can lie or sit on an adult’s lap. Ensure a young child has his/her favourite cuddly toy or comforter with him/her throughout.²,¹³
- Prepare equipment and wash hands, put on apron and sterile gloves.⁴,⁷,¹⁰,¹⁴
- Remove local anaesthetic cream and dressing and clean any residual cream from site.⁵
- Sterilise the site with ChloraPrep Sepp, wait for the area to dry.⁷,¹¹
- Prepare local anaesthetic withdrawing from ampoule with blue needle, inject lignocaine 1% using orange needle. Placement of lignocaine should be intradermally with the majority subcutaneously such that an area 1.5 x 1cm is affected.¹⁴
- Wait 2-3 minutes.
- Clean area vigorously with normal saline using non woven swabs from dressing pack, and dry.
- Pull the skin tight, introduce the punch and rotate 360 degrees with the cutting edge carrying the punch down onto the tissue (the guard will prevent deep penetration).¹⁵
- Withdraw the punch whilst applying pressure to site with a non-woven swab (found in dressing pack).
- Remove specimen using sterile forceps and scissors or scalpel. Without touching the biopsy, transfer immediately into the skin biopsy cryotube. Replace the screw cap.
- Apply pressure to wound with non woven swab until cessation of bleeding
- Apply Steristrips over wound.⁴
- Cover with Mepore or another suitable dressing.⁴
- Provide family with after care instructions, including analgesic dose should this be required.⁴,¹²,¹³
- Dispose of equipment and waste per BCH policy.¹⁴
- Send the sample immediately to the laboratory with a fully completed request form⁴,¹¹ and the lower part of the Skin Biopsy Consent form.

References

1. Olpin S. What are Biopsies, Cultures and Assays and what information do they provide? CLIMB update 2008;3:11-14
2. NMC. Professional code of conduct. April 2008.
8. BCH. Consent, Tissue and Bodily fluids policy. 2006.
9. BCH. Seeking and obtaining consent to treatment, examination and research with Children, Young People and those with “Parental Responsibility”. February 2006.
10. BCH. Policy for effective and appropriate hand hygiene. October 2006.
14. BCH. Policy for the management of risks associated with needle stick injuries and mucous membrane exposures to blood and body fluids. January 2007
APPENDIX B: Guidelines for Emergency Specimen Collection (Inherited Metabolic Disorder Suspected)

In life-threatening situations, where an inherited disorder is thought to be likely (either from family history, results of preliminary investigations or clinical presentation) appropriate specimens should be collected. At the earliest opportunity contact the metabolic laboratory duty biochemist (0121 333 9864) to discuss appropriate investigations. If possible, urine and blood specimens should be taken before death. Skin and tissue specimens, if not taken pre-mortem, should be taken as soon as possible after death. If any of the samples are taken after death it is extremely important to record accurately both the time of death and when the samples were taken. Appropriate storage as detailed below is essential. Local laboratories should make arrangements for suitable storage and transport of tissues to the specialist laboratory.

**Urine**
Urine, however little is extremely useful. Ideally 5-10ml should be stored. Collect into a bottle with no preservative and store deep frozen (-20°C or lower). If the specimen is contaminated with blood, centrifuge to remove cells before freezing the supernatant.

**Blood**
Collect 5-10ml in lithium heparin and 0.5ml in fluoride oxalate: separate the plasma as soon as possible and store the plasma deep frozen (-20°C). Store the packed red cells at +4°C (do not freeze). If DNA analysis is likely to be required, store a further 5-10ml of whole blood (EDTA) in a plastic tube at +4°C.

**Skin (for fibroblast culture)**
Skin taken up to 24 hours after death is likely to be viable provided it is not infected. Take a skin biopsy and place it in tissue culture medium which is available from us or a suitable transport medium (obtainable from most Virology or Cytogenetics Departments). In emergency, sterile isotonic saline can be used, but do not use agar. The specimen should be stored at +4°C before despatch. Do not freeze. See Appendix A for further details. Transport to BCH by taxi or hospital transport to reach us within 24 hours of collection. Sterility is of paramount importance when taking skin biopsy specimens, especially at necropsy. Tissue culture medium and a protocol are available on request.

**Tissue specimens (liver, heart muscle, skeletal muscle, duodenum)**
Please ensure that these specimens are labelled with the type of tissue as well as the patient details.

Label the tubes prior to taking the specimens. Biopsies should only be taken if there is a strong clinical suspicion of a primary defect in one of these tissues. It is very important that blood and urine specimens are also taken and not just tissue specimens. Necropsy tissue specimens are suitable usually only for biochemical analysis if taken within two hours of death.

Two or three needle biopsy specimens of tissue should be taken and placed in a small plastic tube. Immediately place a small piece of plastic film over the top of the specimen to prevent the biopsy drying out, cap the tube and snap freeze in liquid nitrogen (or solid CO₂) and store in the coldest freezer available. If liquid nitrogen or solid CO₂ are not available specimens must be stored immediately in the coldest freezer available. Please note that the collection procedures for tissue for biochemical analyses are not necessarily appropriate for histological tests and your local Histopathology Department should be contacted if specimens are required for histological analysis. Please contact the IMD service before sending samples and transport frozen specimens on solid CO₂ (dry ice).

**Cerebrospinal fluid**
Sometimes a cerebrospinal fluid specimen may be useful. Collect a 1ml specimen. If blood stained, centrifuge and separate the supernatant. Store deep frozen.
APPENDIX C: Sudden Unexplained Deaths in INFANCY (SUDI)

**SUDI investigations should be carried out** in all children less than 2 years of age who die *suddenly* and whose death is *unexplained*. This covers the investigation for:

- Inherited Metabolic Disorders
- Police Purposes (i.e. Forensic Laboratory and Radiology)

in children who die

- at home
- en route/shortly after arrival at hospital
- in hospital (Coroner’s case)

**Summary of Samples Required**

**Blood** (heart stab) for;

**Blood culture (Pedplus/F)** – *Pedplus/F bottles* are designed to take 0.5 – 5.0ml blood. The greater the sample volume, the more likely that bacteraemia can be detected.

**Lithium heparin specimen** (at least 0.5ml)

**Guthrie card spots** – These should ideally be prepared using fresh non-anticoagulated blood. *From the syringe* place 4 drops of blood directly onto a labelled neonatal screening blood test card provided in the SUDS kit.

**Urine** (bladder stab)

Place into a sterile plastic universal container. If urine is unobtainable, but the nappy is wet, place the nappy in a plastic bag, seal and label.

**Naso-pharyngeal swab** for virology

The swab should be cut off, using scissors, into a bottle of viral transport medium.

**Skin** for fibroblast culture.

See the guidelines for skin biopsy protocol (Appendix A)

At BCH, medium for skin biopsies are located in the refrigerator outside the resuscitation room in the emergency department.

**Tests carried out will be:**

<table>
<thead>
<tr>
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<th>Tests Conducted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>acyl carnitines, quantitative amino acids</td>
</tr>
<tr>
<td>Blood spots</td>
<td>acyl carnitines</td>
</tr>
<tr>
<td>Urine</td>
<td>depends upon specimen volume; if &gt;5 mL organic acids will be analysed</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>will be banked for subsequent fibroblast culture if indicated by metabolic results, if not cultured, all biopsies are stored for 3-4 months and then discarded</td>
</tr>
</tbody>
</table>
APPENDIX D: Laboratories to which Tests are Routinely Referred

Metabolites and Enzymes

Addenbrookes Hospital
Biochemical Genetics Unit
Box 247
Hills Road
Cambridge, CB2 2QQ

University College London Hospitals
Department of Clinical Biochemistry
60 Whitfield St
London
W1T 4EU

Great Ormond Street Hospital
Department of Chemical Pathology
Great Ormond Street
London
WC1N 3JH

Bristol Royal Infirmary
Department of Clinical Biochemistry
Bristol
BS2 8HW

University Hospital of Wales
Department of Medical Biochemistry
Heath Park
Cardiff
CF14 4XW

Kings College Hospital
Dept of Clinical Chemistry
Denmark Hill
London
SE5 9RS

Sheffield Childrens Hospital
Department of Clinical Chemistry
Western Bank
Sheffield
S10 2TH

Pole Biologie-Pathologie-Pharmacie
Service de Virologie
Bâtiment Jean Dausset - 6 étage, Hopital Cochin
27 rue du Faubourg Saint Jacques
Paris
France

Guy’s & St Thomas’ Hospital,
Purine Research Laboratory
4th Floor
North Wing
Westminster Bridge Road
London
SE1 7EH

Academisch Medisch Centrum
Laboratorium Genetische Metabole Ziekten
Room FO-132A
Meibergdreef 9
Amsterdam
The Netherlands

Neurometabolic Unit
Box 105
National Hospital (UCLH Trust)
Queen Square
London
WC1N 3BG

Potsdam MVZ GbR
Institute fuer Medizinische Diagnostik Berlin
Nicolaistrasse 22
Berlin
Germany

Southmead Hospital
Department of Clinical Biochemistry
Blood Sciences Laboratories
Southmead Hospital
Bristol
BS10 5NB
APPENDIX D cont’d: Laboratories to which Tests are Routinely Referred

**Molecular tests**

**West Midlands Regional Genetics Laboratory**  
Birmingham Womens Hospital NHS Trust  
Metchley Park Road  
Edgbaston  
Birmingham  
B15 2TG

**London North East Thames RGC (Great Ormond Street Hospital)**  
NE Thames Regional Molecular Genetics Laboratory  
Great Ormond Street Hospital NHS Trust  
Level 6 York House  
37 Queen Square  
London  
WC1N 3BH

**Sheffield Diagnostic Genetics Service (Molecular)**  
Sheffield Children's NHS Foundation Trust  
Western Bank  
Sheffield  
S10 2TH

**DNA Laboratory, GSTS Pathology**  
Genetics Centre, 5th floor, Tower Wing  
Guy’s Hospital  
Great Maze Pond  
London  
SE1 9RT

**Oxford RGC**  
Oxford Radcliffe Hospitals NHS Trust  
The Churchill  
Old Road,  
Headington  
Oxford  
OX3 7LJ

**Department of Clinical Genetics - VU University Medical Center (Amsterdam)**  
Laboratorium voor DNA en Eiwitdiagnostiek  
De Boelelaan 1117  
NL-1081 HV Amsterdam  
NETHERLANDS

**Newcastle Mitochondrial NSCAG Diagnostic Laboratory**  
Mitochondrial Research Group  
4th Floor, The Medical School  
Newcastle University,  
Framlington Place  
Newcastle upon Tyne  
NE2 4HH

**Yorkshire RGC (Leeds)**  
Yorkshire Regional DNA Laboratory  
Ashley Wing  
St James's University Hospital  
Leeds  
LS9 7TF

**West of Scotland Regional Molecular Genetics Laboratory (Glasgow)**  
Duncan Guthrie Institute of Medical Genetics,  
Yorkhill Hospital  
Dalnair Road  
Glasgow  
G3 8SJ