UKAS MEDICAL 9027

The Newcastle upon Tyne Hospitals NHS Foundation Trust

USER MANUAL
Newcastle Highly Specialised Mitochondrial Diagnostic Service

Wellcome Centre for Mitochondrial Research, 4th Floor Cookson Building, The Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH
Telephone: 0191-2824375
www.mitoresearch.org.uk e-mail: tnu-tr.newcastle-mitochondria@nhs.net

General Laboratory Information

Location: Main laboratory Room M4012, Medical School
Main Office Room M4028, Medical School

Service Hours: Monday – Friday: 08:00 to 17:00

Head of Laboratory: Professor Rob Taylor (Tel: 0191-2083685 direct line)
E-mail: robert.taylor27@nhs.net

Deputy Head of Laboratory: Dr Emma Watson (Tel: 0191-2824607)
Email: emma.watson33@nhs.net

Clinical Service (Adults): Dr Grainne Gorman (Tel: 0191-2824375)
E-mail: grainne.gorman@nhs.net
Dr Andrew Schaefer (Tel: 0191-2824375)
E-mail: andrew.schaefer@nhs.net
Professor Doug Turnbull (Tel: 0191-2824375)
E-mail: doug.turnbull@nhs.net

Clinical Service (Children): Professor Robert McFarland (Tel: 0191-2824375)
E-mail: robert.mcfarland2@nhs.net

Clinical Scientists: Dr Charlotte Alston (Tel: 0191-2088877)
Miss Jacqueline Didcock (Tel: 0191-2088877)
Dr Langping He (Tel: 0191-2088877)
Miss Charlotte Knowles (Tel: 0191-2088877)
Ms Eleni Mavraki (Tel: 0191-2088877)

Biomedical Scientists: Mr Gavin Falkous (Tel: 0191-2088877)
Mrs Sila Hopton (Tel: 0191-2088877)

Genetic Technologist: Mrs Karen Baty (Tel: 0191-2088877)
Dr Kate Hickman (Tel: 0191-2088877)
Miss Roseanne Jones (Tel: 0191-2088877)
Miss Sarah Smith (Tel: 0191-2088877)

Senior Healthcare Assistant: Mrs Victoria McClurey (Tel: 0191-2088877)

Quality Manager: Mr Amritjit Singh (Tel: 0191-2231019)
E-mail: amritjit.singh@nhs.net

Service Administrator: Mrs Sue Callender (Tel: 0191-2824375)
E-mail: susan.callender@nhs.net

Date of original issue: March 2007
Revised version 9.6
Date of Revision 26.02.20

Background Information to the Service

Mitochondria are ubiquitous organelles that contain their own genetic complement, the mitochondrial genome (mtDNA). Although intimately involved in many cellular processes, their principal task is to provide the energy necessary for normal cell functioning and maintenance. Disruption of this energy supply can have devastating effects for the cell, organ and individual. One important consequence of mitochondrial ubiquity is that mitochondrial disease can affect virtually any organ and present with a plethora of symptoms and signs to a variety of specialties. These are truly multi-system diseases with significant morbidity and mortality. Over the last two decades, mutations in both mtDNA and nuclear DNA (nDNA) have been identified as causative in a number of the mitochondrial clinical syndromes, although for mtDNA mutations in particular, this relationship between genotype and phenotype is often far from straightforward. A number of epidemiological studies have been undertaken to assess the prevalence of mitochondrial disease and whilst rare these conditions have a major impact on both the community and individual families. Finally, there is increasing awareness by clinicians experienced in the management of patients with mitochondrial disease that many aspects of mitochondrial disease can be helped or prevented by early diagnosis and subsequent care.

The Newcastle Mitochondrial Diagnostic Laboratory is an affiliated laboratory of the Northern Regional Genetics Service, and is situated within the research laboratory space of the University's Wellcome Centre for Mitochondrial Research in the Medical School. In partnership with teams at Queen Square, Institute of Neurology (UCLH NHS Foundation Trust) and the Oxford Medical Genetics Laboratories, Churchill Hospital (Oxford Radcliffe Hospitals NHS Trust), the Newcastle lab has been awarded National Specialist Commissioning funding to provide a comprehensive, diagnostic and clinical management service for patients with mitochondrial disease in England and Scotland – "***Rare Mitochondrial Disorders Service for Adults and Children***". This multi-disciplinary service will encompass all aspects of diagnosis (muscle biopsy, histochemistry, biochemistry and molecular genetics), utilising specialist clinical and laboratory skills available at the three component centres, and complementing the routine analysis of common mtDNA mutations that is available throughout the UK at many regional genetics laboratories. For many patients with suspected mitochondrial disease, it is not possible to make a diagnosis based solely on molecular genetic testing in blood DNA, and so for those patients where more detailed investigations are required, a comprehensive diagnostic service is now offered which combines clinical investigations, histochemical and histological analysis of patient muscle biopsies, measurement of respiratory chain complex activities together with screening of both mtDNA and nuclear-encoded mitochondrial genes using next-generation sequencing technologies. The laboratory is integrated within the Wellcome Centre for Mitochondrial Research at Newcastle University (http://www.newcastle-mitochondria.com) and also offers research-based whole exome sequencing as well as participating in the Genomics England 100,000 Genomes Project (https://www.genomicsengland.co.uk).

Services offered by the Newcastle Highly Specialised Mitochondrial Diagnostic Laboratory

CLINICAL SERVICES

Outpatient

Consultations are available for patients and families with suspected or proven mitochondrial disease. Clinical examination may confirm the suspicion of mitochondrial disease or suggest an alternative diagnosis. Clear plans of investigation or patient management will be established during the clinic appointment with close collaboration between the referring consultant and the patients own general practitioner. Whenever possible, follow up will be at local hospitals, although some patients with particularly rare conditions or where local services are limited may require longer term follow up in Newcastle.

Consultations are also available for women with proven mtDNA disease or who are carriers of pathogenic mtDNA mutations and who require advice concerning the possible transmission of the mtDNA mutation to their children. Patients or families in which mitochondrial respiratory chain disease is confirmed but in whom the genetic diagnosis has not been established, or with mutations in known nuclear genes, also have access to this service.

Inpatient

Day-case and inpatient services are available for patients who have to travel for specific diagnostic investigations, and are available for both children and adults. Muscle biopsies are not always available in certain hospitals and these can be arranged to be performed in Newcastle as part of the diagnostic work-up.

Nurse Consultant: Catherine Feeney (Tel: 0191-2821740)
E-mail: catherine.feeney1@nhs.net

Nurse Specialist: Alex Bright (Tel: 0191 208 3008)
E-mail: alexandra.bright1@nhs.net

Secretaries: Jane Brown (jane.brown50@nhs.net)
Bernadette Caygill (bernadette.caygill@nhs.net)

For clinicians wishing to refer patients for a clinical opinion (either as outpatients or inpatients), please write to Dr Gorman (adult referrals) or Dr McFarland (paediatric referrals) at the following address:

Newcastle Highly Specialised Mitochondrial Diagnostic Laboratory
Wellcome Centre for Mitochondrial Research
4th Floor Cookson Building
The Medical School
Newcastle University
Framlington Place
Newcastle upon Tyne
NE2 4HH
Tel. 0191-2824375
Email: susan.callender@nhs.net

LABORATORY SERVICES

Histological and Histochemical analysis of muscle biopsy samples

Date of original issue: March 2007
Revised version 9.6
Date of Revision 26.02.20

An unfixed frozen muscle sample, in transverse orientation, measuring approximately **3mm x 3mm x 3mm (25 mg) is the minimum** required for mitochondrial histochemical analysis, which will include cytochrome *c* oxidase (COX) reactions, succinate dehydrogenase (SDH) reactions and sequential COX-SDH assays to thoroughly investigate the possibility of low levels of COX-deficient fibre. As appropriate in specific cases, other tissues are accepted for the investigation of mitochondrial histochemical activities including heart (e.g. suspected mitochondrial cardiomyopathies) and liver (e.g. Alpers' Syndrome). Details for the dispatch of frozen tissues are given later in this manual.

Respiratory chain enzyme measurements in muscle biopsy samples

To fully assess mitochondrial respiratory chain activity in frozen tissue samples, we assay the activities of respiratory chain complexes I, II, III and IV individually and compare these activities to the activity of the mitochondrial matrix marker enzyme citrate synthase, an indicator of mitochondrial mass within the sample.

An unfixed, snap-frozen muscle sample is required for these investigations, preferably unmounted and free from OCT and cork. Ideally, between **100-150mg muscle tissue** is preferred to be able to perform these assays with **60mg tissue the absolute minimum amount** of sample we will accept. If only orientated tissue blocks are available for muscle biopsies, we may be able to assess respiratory chain function in these using quantitative immunohistochemistry.

Molecular genetic analysis for suspected mitochondrial disorders

The Newcastle Mitochondrial Diagnostic Laboratory follows advice given by the Joint Committee on Genomics in Medicine report "Consent and Confidentiality in Genomic Medicine (3rd edition)" that the responsibility for obtaining consent for genomic testing is placed on the clinician. The report gives an example of a template form that may be used (appendix 1) and points that should be covered in this discussion.

The laboratory offers a range of tests for both mtDNA mutations, ranging from point mutation analysis to whole mitochondrial genome sequencing, and the analysis of several nuclear genes involved in mtDNA maintenance. For many common mtDNA point mutations, genetic screening can be undertaken using blood DNA, although the use of alternative sources such as urinary cell sediment DNA samples are recommended for some mutations, in particular the m.3243A>G mutation. For the study of possible mtDNA rearrangements and whole mitochondrial genome, muscle DNA is essential.

Samples for genetic analysis:

Muscle: If a muscle biopsy is already being referred for either histochemical or biochemical assessment, we are able to extract DNA either directly from cryostat-cut sections or from a residual, nuclear pellet generated during the preparation of an enriched mitochondrial fraction for enzyme studies. The details for dispatch of muscle biopsy samples on dry ice are given later in this manual.

Blood: Extracted DNA or 2-3 x 4.5ml EDTA-blood (purple top) tubes should be sent for analysis; please use EDTA as anticoagulant rather than heparin, which precludes molecular genetic testing. Mix the blood well after taking, but do not freeze; these samples can be stored at 4°C for 1-2 days if required without problems, and should be shipped at room temperature.

Urine: Urine samples (40-50ml) should be collected into sterile universal or falcon-type tubes and forwarded to the lab at room temperature; do not freeze. To

ensure the best possible yield of epithelial cells from these samples, an early morning urine sample (first pass) is preferable.

Other tissues: Other tissue samples can be accepted for DNA analysis, including pathology blocks, cultured cells, buccal mouth scrapes and hair samples. The investigation of several, non-invasive DNA samples can be particularly useful in determining the pathogenic behaviour of specific (or novel) mtDNA mutations. Please contact the laboratory for specific instructions as to what we require and how to send these samples.

NOTE: Any remaining sample/DNA is currently retained in long term storage and may be used anonymously unless otherwise stated on the request form.

Sample Labelling

All samples referred to the laboratory should be clearly labelled with at least two unique patient identifiers and should be accompanied by a completed laboratory referral form. Where known, the identity of the person who has collected the primary sample, along with the collection date should be recorded on the accompanying referral form. Requests for copies of the referral form should be made to susan.callender@nhs.net.

Please forward the samples along with a completed laboratory referral form to:
Professor Rob Taylor, Newcastle Highly Specialised Mitochondrial Diagnostic Laboratory Wellcome Centre for Mitochondrial Research, 4th Floor Cookson Building, The Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH

Samples are classified as UN 3373 Category B Diagnostic specimens and must be transported in accordance with this classification (49 CFR, Part 173.199 or IATA Packing Instruction 650).

NOTE: We are not able to accept samples designated, or suspected, as being "High Risk" (i.e. from patients with HIV, hepatitis, CJD, polio etc.)

MUSCLE BIOPSY - DISPATCH INSTRUCTIONS

1. **Please inform the Service Administrator or laboratory of your intention to send a sample on dry ice before it leaves your laboratory, either by phone or by e-mail. Please note: we cannot accept responsibility for the safe receipt of samples sent without the prior knowledge of our unit.**

2. When you send the samples, please include a covering letter with the names and addresses of any additional people who will require copies of letters or reports and a completed referral form. More clinical information is always helpful, in addition to that provided on the referral form. Additionally, please send a copy of the muscle histopathology report, if available.

3. The muscle sample must be sent in dry ice, using a recognised courier (e.g. TNT or FedEx) for 'door to door' delivery. A "next day before 12 noon" delivery service should be used. Please ensure that sufficient dry ice is used to last 48 hours (at least 10kg, but dependent on size of polystyrene container). Ensure that no absorbent material is insulating the primary vessel from the dry ice. Do not use polystyrene chips or freezing blocks to fill the polystyrene container.

4. Address to: **Professor Rob Taylor**
   Newcastle Highly Specialised Mitochondrial Diagnostic Laboratory
   Wellcome Centre for Mitochondrial Research
   4th Floor Cookson Building
   The Medical School
   Newcastle University
   Framlington Place
   Newcastle upon Tyne
   NE2 4HH

   It is helpful to place address labels on more than one side of the box as the courier usually puts their own label on top.

5. Please try and send samples on a Monday, Tuesday or Wednesday. Do not send samples to arrive on a Friday, since delays may well move the delivery of your package into the weekend. Our unit is not staffed at these times; therefore your sample will thaw and be lost.

Date of original issue: March 2007
Revised version 9.6
Date of Revision 26.02.20

Current list of tests available at the Newcastle Highly Specialised Mitochondrial Diagnostic Laboratory

Please contact the lab directly if further details are required.

HISTOLOGICAL/HISTOCHEMICAL ANALYSES

Each frozen sample is assessed for the following:

- H&E staining of cryostat-cut sections
- Cytochrome *c* oxidase (COX) activity
- Succinate dehydrogenase (SDH) activity
- Sequential COX-SDH activities
- Modified Gomori trichrome staining

MITOCHONDRIAL RESPIRATORY CHAIN ANALYSES

Each frozen sample is assessed for the following:

- Complex I (NADH:ubiquinone oxidoreductase) activity
- Complex II (Succinate:ubiquinone oxidoreductase) activity
- Complex III (Ubiquinol:cytochrome *c* oxidoreductase) activity
- Complex IV (Cytochrome *c* oxidase) activity
- Citrate Synthase

MITOCHONDRIAL IMMUNOHISTOCHEMICAL ANALYSIS

Each frozen sample is assessed for the following:

- Complex I expression (NDUFB8 labelling)
- Complex IV expression (COXI loading)
- Mitochondrial content (Porin labelling)

MOLECULAR GENETIC ANALYSES

(This list is not exhaustive please contact the laboratory to discuss testing not listed)

MUTATION/DISORDER TO BE TESTED	TYPE OF TEST/ SAMPLE NEEDED
m.3243A>G (MELAS syndrome, maternally-inherited diabetes and deafness (MIDD))	Pyrosequencing to allow estimation of mtDNA heteroplasmy. Blood and/or urine DNA; muscle if available.
m.1555A>G	Sanger sequencing of the relevant region of the mitochondrial *MTRNR1* (12S rRNA gene). Blood DNA appropriate.
m.8344A>G, m.8356T>C and m.8363G>A (MERRF syndrome)	Sanger sequencing of entire *MTTK* ($tRNA^{Lys}$) gene for known pathogenic mutations. Blood DNA or muscle if available.
m.8993T>G/C and m.9176T>G/C (NARP and MILS (maternally-inherited Leigh Syndrome))	Sanger sequencing of the mitochondrial *MTATP6* and *MTATP8* genes. Blood DNA appropriate.

Date of original issue: March 2007
Revised version 9.6
Date of Revision 26.02.20

MUTATION/DISORDER TO BE TESTED	TYPE OF TEST/ SAMPLE NEEDED
LHON	Screening of 3 primary LHON mutations (m.3460G>A, m.11778G>A and m.14484T>C) by Sanger sequencing. Blood DNA appropriate.
Maternally inherited deafness (*MTRNR1* (12S rRNA) gene including m.1555A>G mutation and *MTTS1* ($tRNA^{Ser(UCN)}$ gene))	Sanger sequencing of both genes. Blood DNA appropriate.
***MTCYB* gene sequencing** (patients with isolated complex III deficiency)	Sanger sequencing of mitochondrial-encoded cytochrome *b* gene. DNA from affected tissue (e.g. muscle) essential.
Mitochondrial genome sequencing (Screen for rare or novel pathogenic mtDNA mutations by Ion Torrent next generation sequencing)	DNA from affected tissue (e.g. muscle) essential for adults although blood DNA may be suitable for children.
mtDNA rearrangement disorders (CPEO, Kearns-Sayre, Pearsons syndrome)	Long-range PCR of affected tissues to investigate single mtDNA and secondary multiple mtDNA deletions. Muscle DNA essential for adults; blood DNA suitable for children with Pearsons syndrome.
Single fibre real-time PCR (Quantification and screening of mtDNA rearrangements in individual muscle fibres (COX-deficient and COX-positive) by real-time PCR)	A unfixed frozen muscle biopsy sample is required, in transverse orientation to allow histochemical analysis and isolation of single cells by laser microdissection.
mtDNA depletion syndromes (Assessment of mtDNA copy number to screen for possible mtDNA depletion syndromes)	Taqman® real-time PCR assay which coamplifies nuclear (18S rRNA) and mtDNA (*MTND1*) genes. DNA from affected tissues (e.g. muscle, liver) essential.
POLG (*POLG* mutations cause a phenotypic spectrum ranging from severe encephalopathy and liver failure typical of Alpers syndrome to late-onset PEO, ataxia, myopathy and epilepsy associated with multiple mtDNA deletions and depletion)	Screening for the three common, c.1399G>A p.(Ala467Thr), c.2243G>C p.(Trp748Ser) and c.2542G>A p.(Gly848Ser), *POLG* mutations by pyrosequencing and/or Sequencing of the entire *POLG* coding region. Blood DNA appropriate.
AARS2 (Patients with multiple respiratory chain complex deficiencies and hypertrophic cardiomyopathy)	Sequencing of the entire *AARS2* coding region. Blood DNA appropriate.

MUTATION/DISORDER TO BE TESTED	TYPE OF TEST/ SAMPLE NEEDED
***ACAD9* – complex I assembly factor** (Patients with isolated complex I deficiency; often associated with cardiac phenotype)	Sequencing of the entire *ACAD9* coding region. Blood DNA appropriate.
AGK (Patients with multiple respiratory chain complex deficiencies and Sengers syndrome (cataracts, HCM and elevated lactate))	Sequencing of the entire *AGK* coding region. Blood DNA appropriate.
DARS2 (Patients with mitochondrial leukoencephalopathy, brain stem and spinal cord involvement, lactic acidosis (LBSL))	Sequencing of the entire *DARS2* coding region. Blood DNA appropriate.
DGUOK* and *MPV17 (Patients with evidence of mtDNA depletion in liver)	Sequencing of the entire *DGUOK* and *MPV17* coding regions. Blood DNA appropriate.
MTO1 (Patients with multiple respiratory chain complex deficiencies, hypertrophic cardiomyopathy and and elevated lactate)	Sequencing of the entire *MTO1* coding region. Blood DNA appropriate.
NFU1 (Patients with multiple respiratory chain complex deficiencies (complex I, III and III) – FeS cluster scaffold gene defect)	Sequencing of the entire *NFU1* coding region. Blood DNA appropriate.
POLG2 (Patients with dominant PEO and multiple mtDNA deletions)	Sequencing of the entire *POLG2* coding region. Blood DNA appropriate.
RARS2 (Patients with multiple respiratory chain complex deficiencies and pontocerebellar hypoplasia)	Sequencing of the entire *RARS2* coding region. Blood DNA appropriate.
***SLC25A4* (ANT1)** (Patients with dominant PEO and multiple mtDNA deletions)	Sequencing of the entire *SLC25A4* coding region. Blood DNA appropriate. .
SUCLA2* and *SUCLG1 (Patients with evidence of mtDNA depletion and methylmalonic aciduria)	Sequencing of the entire *SUCLA2* and *SUCLG1* coding regions. Blood DNA appropriate.
TK2* and *RRM2B (Patients with dominant/recessive PEO and multiple mtDNA deletions or patients with evidence of mtDNA depletion in skeletal muscle)	Sequencing of the entire *TK2*/*RRM2B* coding regions. Blood DNA appropriate.

MUTATION/DISORDER TO BE TESTED	TYPE OF TEST/ SAMPLE NEEDED
TMEM70, ATPAF2* and *ATP5E (Patients with suspected complex V deficiency)	Sequencing of the entire coding regions of the *TMEM70*, *ATPAF2* and *ATP5E* genes. Blood DNA appropriate.
TRMU (Patients with evidence of acute liver disease and respiratory chain deficiency)	Sequencing of the entire *TRMU* coding region. Blood DNA appropriate.
***TWNK* (Twinkle)** (Patients with dominant/recessive PEO and multiple mtDNA deletions)	Sequencing of the entire *TWNK* coding region. Blood DNA appropriate.
Complex II structural and assembly genes (Patients with evidence of isolated complex II deficiency)	Sequencing of the entire coding regions of the four structural genes (*SDHA*, *SDHB*, *SDHC*, *SDHD* and known assembly factors *SDHAF1* and *SDHAF2*). Blood DNA appropriate.
Nuclear complex III genes (Patients with isolated complex III deficiency)	Sequencing of the entire coding region of eleven, highly conserved nuclear-encoded complex III genes for mutations causing isolated complex III deficiency. Blood DNA appropriate.
Targeted NGS for Nuclear complex I structural genes and assembly factors (n=49) and mtDNA maintenance genes (n=18)	Please contact Professor Taylor for further information. Blood DNA appropriate.
Whole exome sequencing	Please contact Professor Taylor and Professor McFarland to discuss individual cases.
CVB and prenatal testing for nuclear and mtDNA mutations	Please contact Professor Taylor to discuss individual cases – please note that there is a charge applicable for this testing as this is not covered under our specialist funding agreement.
PGD for specific mtDNA mutations	Please contact Professor Taylor and Professor McFarland to discuss individual cases - please note that there is a charge applicable for this testing as this is not covered under our specialist funding agreement.
Mitochondrial Donation	Please contact Dr Grainne Gorman to discuss individual cases – please note a charge will be applicable for this service for referrals outside of England, Scotland and Northern Ireland.

Sample Reporting Times

Please contact the laboratory for guidance on sample reporting times if <u>urgent</u> analysis is required.

Histological/Histochemical analysis	14 calendar days
Respiratory Chain Enzyme analysis	56 calendar days
Immunohistochemistry	56 calendar days
Prenatal analysis	3 calendar days
Predictive testing	14 calendar days
Non-urgent known variant testing	42 calendar days
Mitochondrial gene analysis (per gene)	42 calendar days
Mitochondrial genome sequencing (NGS)	84 calendar days
***POLG* sequencing**	42 calendar days
Nuclear gene analysis (per gene)	42 calendar days
Targeted nuclear gene panels (NGS)	84 calendar days

External Quality Control

We participate in the following external quality assessment schemes.

- **GenQA (Mitochondrial disorders including *POLG*, Pathogenicity of sequence variants (interpretation only) and Next Generation Sequencing Germline (pilot))**
- **European Molecular Genetics Quality Network (Full Sanger Sequencing Scheme)**
- **UKNEQAS for Cytopathology Technique**

There are currently no external schemes available in the UK for mitochondrial respiratory chain enzyme analysis and mitochondrial DNA depletion; therefore we have developed an annual sample exchange programme with Dr Amanda Lam at UCLH mitochondrial respiratory chain enzyme analysis and Mr Carl Fratter at the Oxford Regional Genetics Laboratory for mitochondrial DNA depletion.

User Satisfaction Survey for Laboratory Services

As part of our quality management system and to ensure that we are meeting the needs of our users, we are always keen to receive any comments you may have on the quality of the service we provide and would welcome any suggestions on ways in which we might be able to improve the service.

Please feel free to contact the laboratory Quality Manager (amritjit.singh@nhs.net) with any suggestions; an electronic questionnaire is available directly by email should this be required.

Accreditation Status

The Newcastle Mitochondrial Diagnostic Service Laboratory is accredited by the United Kingdom Accreditation Service (UKAS) Ltd for ISO 15189:2012 Medical Laboratories and operates a quality management system in accordance with UKAS standards for the Medical Laboratory.

UKAS reference 9027

National Genomic Test Directory

From 1st October 2018 the National Genomic Test Directory will specify which genomic tests are commissioned by the NHS in England, the technology by which they are available, and the patients who will be eligible to access to a test. The final draft 2018/2019 National Genomic Test Directory for rare and inherited disorders and cancer can be accessed at https://www.england.nhs.uk/publication/national-genomic-test-directories. The Newcastle Mitochondrial Diagnostic Service Laboratory is one of three laboratories commissioned by NHSE to provide highly specialised mitochondrial genetic testing as specified by the National Genomic Test Directory.