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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)
E-mail: robert.taylor27@nhs.net

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

Rare Disease Service Lead: Dr Charlotte Alston (Tel: 0191 2088877)
E-mail: charlotte.alston1@nhs.net

Clinical Service (Adults): Dr Andrew Schaefer (Tel: 0191 2824375)
E-mail: andrew.schaefer@nhs.net

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

Clinical Scientists: Mr Jack Baines (Tel: 0191 2088877)
Dr Langping He (Tel: 0191 2088877)
Mrs Charlotte Hemingbrough (Tel: 0191 2088877)
Ms Eleni Mavraki (Tel: 0191 2088877)

Trainee Clinical Scientists: Dr Kate Hickman (Tel: 0191 2088877)
Miss Sarah Smith (Tel: 0191 2088877)

Biomedical Technologist: Mrs Sila Hopton (Tel: 0191 2088877)

Genetic Technologist: Mrs Lauren Johnson (Tel: 0191 2088877)
Miss Roseanne Steel (Tel: 0191 2088877)
Miss Vidushi Aggarwal (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

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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 three decades, pathogenic variants in both mtDNA and nuclear DNA (nDNA) have been identified as causative in numerous mitochondrial clinical syndromes, although for mtDNA variants 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 a component laboratory of the North East and Yorkshire GLH and is integrated within the Wellcome Centre for Mitochondrial Research at Newcastle University (http://www.newcastle-mitochondria.com. In partnership with teams at GOSH (North Thames GLH) and Oxford (Central and South GLH), the Newcastle laboratory has 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 encompasses many aspects of diagnosis (histochemistry, immunohistochemistry, biochemistry and genomics), utilising specialist clinical and laboratory skills available at the three component centres. 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 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.

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 known to harbour a pathogenic mtDNA variant and who require advice concerning the possible transmission of the mtDNA variant 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 pathogenic variants 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

Administrator: Jane Brown (jane.brown50@nhs.net)

For clinicians wishing to refer patients for a clinical opinion (either as outpatients or inpatients), please write to Dr Andrew Schaefer (adult referrals) or Professor Robert 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: jane.brown50@nhs.net

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LABORATORY SERVICES

Histological, Histochemical and Immunohistochemical analysis of muscle biopsy samples
An unfixed frozen muscle sample, in transverse orientation, measuring approximately **3mm x 3mm x 3mm (25 mg) is the minimum** required for analysis.
Histochemical investigations 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.
Mitochondrial immunohistochemical analysis uses a quadruple immunohistochemical assay to assess complex I (NDUFB8), complex IV (COX1) and porin (VDAC1) protein expression. Please note that post-mortem tissue is not suitable for immunohistochemcial analysis.

Respiratory chain enzyme measurements in muscle biopsy samples and fibroblasts
To fully assess mitochondrial respiratory chain activity, 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.

Muscle: 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.

Fibroblasts: Either a frozen cell pellet or at least one T25 flask of growing fibroblasts should be referred for analysis. In both instances, the cell line should be confirmed to be free of mycoplasma prior to shipment.

Functional studies to support variant classification – only available following agreement with the Head/Deputy Head of Laboratory and the Rare Disease Service Lead
The laboratory undertakes a range of functional assays to support re-classification of variants of uncertain significance, primarily cDNA investigations to investigate putative splicing variants (UKAS accredited), SDS-PAGE and western blotting to investigate an effect on protein steady state levels, or BN-PAGE and western blotting to investigate the assembly of native OXPHOS complexes (complexes I-V); SDS-PAGE and BN-PAGE is currently offered on a research basis only.

Muscle: An unfixed, snap-frozen muscle sample is required for these investigations, preferably unmounted and free from OCT and cork. For samples requiring BN-PAGE and SDS-PAGE, between **100-150mg muscle tissue** is preferred to be able to perform these assays; where only smaller samples are available, **20mg tissue** would be sufficient for SDS-PAGE analysis only.

Fibroblasts: Either a frozen cell pellet or at least one T25 flask of growing fibroblasts should be referred for analysis. In both instances, the cell line should be confirmed to be free of mycoplasma prior to shipment.

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 assumes, that on receipt of a clinical sample and completed referral form, consent has been obtained by the referring clinician.

Please inform the laboratory immediately if a relevant genetic diagnosis is reached outside of our laboratory to prevent unnecessary testing.

The laboratory offers a range of tests for both mtDNA variants, ranging from targeted single nucleotide analysis and single gene sequencing to whole mitochondrial genome sequencing, and the analysis of large nuclear gene panels associated with mitochondrial disease. For some common mtDNA variants, genetic screening can be undertaken using blood DNA, although the use of alternative sources such as urinary epithelial cell DNA samples are recommended for some variants, in particular *MT-TL1* m.3243A>G. For the study of possible mtDNA rearrangements and whole mitochondrial genome sequencing, muscle DNA is recommended in adult patients. Please see specific test details provided below or contact the laboratory if further advice is required.

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 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 a 4-5ml EDTA-blood tube 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 tube 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 strongly recommended and it is advised that the sample should reach the laboratory within 72 hours of collection.

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

NOTE: Samples requiring only DNA analysis should be sent to your local genetics laboratory for extraction wherever possible; your local genetics laboratory will then forward a DNA sample to the laboratory for testing. Any remaining sample/DNA will be retained in long term storage and may be used anonymously for control purposes 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 tnu-tr.newcastle-mitochondria@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 to ensure that samples are sent 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 and our unit is not staffed at these times.

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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
- 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)

FUNCTIONAL STUDIES TO SUPPORT VARIANT CLASSIFICATION (only available by prior agreement)

- **cDNA studies to investigate putative splicing variants**
  Whole cell lysates derived from growing patient fibroblasts (preferable) or homogenised snap frozen muscle will be subject to RNA extraction and reverse transcription to generate cDNA for analysis. Fresh EDTA blood drawn into a Tempus tube may be appropriate for analysis. cDNA studies are bespoke based upon the gene/variant(s) identified.
- **SDS-PAGE and western blotting**
  Whole cell lysates derived from growing patient fibroblasts or homogenised snap frozen muscle will be subject to SDS-PAGE and western blotting to assess the steady-state levels of target proteins; antibodies used will vary according to putative gene variants identified.
- **BN-PAGE and western blotting**
  Assembly of complexes I-V will be assessed using native PAGE of mitochondria enriched pellets from growing fibroblasts or snap frozen muscle biopsy proceeded by western blotting using antibodies conjugated against each OXPHOS complex.

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MOLECULAR GENETIC ANALYSES

The National Genomic Test Directory specifies which genomic tests are commissioned by the NHS in England, the technology by which they are available and the patients who are eligible to access a test. Full details can be accessed by visiting https://www.england.nhs.uk/publication/national-genomic-test-directories/

Further details and sample specifications for the tests available in our laboratory:

VARIANT/DISORDER TO BE TESTED	TYPE OF TEST/ SAMPLE NEEDED
R42.1 Common LHON variants Leber hereditary optic neuropathy	Screening of m.3460G>A, m.11778G>A and m.14484T>C by Sanger sequencing. Blood DNA appropriate.
R42.2 Mitochondrial genome Leber hereditary optic neuropathy	Screening of the mitochondrial genome. Blood DNA appropriate.
R64.1 *MT-TL1* m.3243A>G (MELAS or maternally-inherited diabetes and deafness (MIDD))	Pyrosequencing to allow estimation of mtDNA heteroplasmy. Blood and/or urine DNA; muscle if available.
R65.1 *MT-RNR1* m.1555A>G	Sanger sequencing of the relevant region of *MT-RNR1*. Blood DNA appropriate.
R299.1 Mitochondrial rearrangements (Possible mitochondrial disorder – mtDNA rearrangement testing)	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.
R299.2 Mitochondrial rearrangements heteroplasmy assessment (Possible mitochondrial disorder – mtDNA rearrangement testing)	Taqman® real-time PCR assay. DNA from affected tissues (e.g. muscle) essential.
R299.3 Mitochondrial rearrangements breakpoint mapping (Possible mitochondrial disorder – mtDNA rearrangement testing)	Long-range PCR and NGS sequencing of affected tissues to determine mitochondrial rearrangement breakpoint. Muscle DNA essential for adults; blood DNA suitable for children with Pearsons syndrome.
R300.1 Mitochondrial genome (Possible mitochondrial disorder - whole mitochondrial genome sequencing)	NGS analysis of the entire mitochondrial genome (mtDNA). DNA from affected tissue (e.g. muscle) recommended for adults; blood DNA may be suitable for children.
R301.1 Mitochondrial depletion (Possible mitochondrial disorder - mtDNA depletion testing)	Taqman® real-time PCR assay which coamplifies nuclear (18S rRNA) and mtDNA (*MT-ND1*) genes. DNA from affected tissues (e.g. muscle, liver) essential.
R350.1 Common MERRF variants (MERRF syndrome)	Sanger sequencing for *MT-TK* m.8344A>G, m.8356T>C and m.8363G>A. Blood DNA or muscle if available.

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R351 *MT-ATP6* and *MT-ATP8* (NARP syndrome or maternally-inherited Leigh Syndrome)	Sanger sequencing of the mitochondrial *MT-ATP6* and *MT-ATP8* genes. Blood DNA appropriate.
R397.1 *MT-TI* m.4300A>G	Sanger sequencing of the relevant region of *MT-TI*. Blood DNA appropriate.
R315.1 Common *POLG* variants (*POLG*-related disorder)	Screening for c.1399G>A p.(Ala467Thr), c.2243G>C p.(Trp748Ser), c.2542G>A p.(Gly848Ser) and c.[752C>T;1760C>T] p.[(Thr251Ile;Pro587Leu)] by pyrosequencing. Blood DNA appropriate.
R315.2 *POLG* (*POLG*-related disorder)	Sequencing of the entire *POLG* coding region and intron-exon boundaries. Blood DNA appropriate.
R316.1 PDH Deficiency (Pyruvate dehydrogenase (PDH) deficiency)	NGS analysis of 24 genes known to be associated with PDH deficiency. Blood DNA appropriate.
R317.1 Mitochondrial liver disease (Mitochondrial liver disease, including transient Infantile liver failure)	NGS analysis of 7 nuclear genes known to be associated with mitochondrial liver disease. Blood DNA appropriate.
R352.1 Mitochondrial DNA maintenance disorder	NGS analysis of 23 nuclear genes known to be associated with a disorder of mitochondrial DNA maintenance. Blood DNA appropriate.
R353.1 Mitochondrial disorder with complex I deficiency	NGS analysis of 50 nuclear genes known to be associated with a disorder of complex I. Blood DNA appropriate.
R354.1 Mitochondrial disorder with complex II deficiency	NGS analysis of 8 nuclear genes known to be associated with a disorder of complex II. Blood DNA appropriate.
R355.1 Mitochondrial disorder with complex III deficiency	NGS analysis of 15 nuclear genes known to be associated with a disorder of complex III. Blood DNA appropriate.
R356.1 Mitochondrial disorder with complex IV deficiency	NGS analysis of 40 nuclear genes known to be associated with a disorder of complex IV. Blood DNA appropriate.
R357.1 Mitochondrial disorder with complex V deficiency	NGS analysis of 19 nuclear genes known to be associated with a disorder of complex V. Blood DNA appropriate.
R63.1 Possible mitochondrial disorder - nuclear	NGS analysis of 311 nuclear genes known to be associated with mitochondrial disease. Blood DNA appropriate.
R394.1 *TYMP* (Mitochondrial neurogastrointestinal encephalomyopathy)	Sequencing of the entire *TYMP* coding region and intron-exon boundaries. Blood DNA appropriate.

R395.1 *SLC19A3* (Thiamine metabolism dysfunction syndrome 2)	Sequencing of the entire *SLC19A3* coding region and intron-exon boundaries. Blood DNA appropriate.
R396.1 *TMEM70* (Mitochondrial Complex V deficiency, TMEM70 type)	Sequencing of the entire *TMEM70* coding region and intron-exon boundaries. Blood DNA appropriate.

Mitochondrial Reproductive Service

Prenatal testing for nuclear and mtDNA variants	Please contact the laboratory to discuss individual cases.
mtDNA PGD	Please contact Professor Grainne Gorman (c/o jane.brown50@nhs.net) to discuss individual cases.
Mitochondrial Donation	Please contact Professor Grainne Gorman (c/o jane.brown50@nhs.net) to discuss individual cases.

Standard Sample Reporting Times

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

Histological/Histochemical analysis	28 calendar days
Respiratory Chain Enzyme analysis	56 calendar days
Immunohistochemistry	56 calendar days
Prenatal analysis	3 calendar days
Predictive testing	14 calendar days
Variant screening or gene sequencing	42 calendar days
Mitochondrial genome sequencing (NGS)	84 calendar days
Targeted nuclear gene panels (NGS)	84 calendar days

External Quality Control

We participate in the following external quality assessment schemes.

- **GenQA: Mitochondrial DNA and *POLG*-related disorders, Pathogenicity of Germline Sequence Variants (classification & interpretation), Variant Validation, Pathogenicity of RNA splicing varints and Next Generation Sequencing Germline**
- **European Molecular Genetics Quality Network: Full Sanger Sequencing Scheme**
- **UKNEQAS: 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 for 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

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.