E13/S(HSS)/h

NHS STANDARD CONTRACT
RARE MITOCHONDRIAL DISORDERS SERVICE (ALL AGES)

PARTICULARS, SCHEDULE 2 – THE SERVICES, A – Service Specification

Service Specification No.	**E13/S(HSS)/h**
Service	Rare mitochondrial disorders service (All Ages)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

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 involvement in all cell types is that mitochondrial disease can affect virtually any organ and present with a plethora of symptoms and signs to a variety of specialties. These genuinely multi-system diseases are associated with significant morbidity and mortality. Over the last two decades, mutations in both mtDNA and nuclear DNA (nDNA) have been shown to be responsible for numerous 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.

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. Multidisciplinary team care including screening for recognized potential complications such as cardiac problems, diabetes, cataracts and renal impairment reduces morbidity and mortality. Further details relating to the clinical features, diagnosis, management, reproductive options and treatment of adult and childhood patients with mitochondrial genetic disease are given in the accompanying review articles which have recently been written by key staff at centres (Rahman and Hanna, *J. Neurol. Psych. Neurosurg.* 2009; McFarland, Taylor

and Turnbull, *Lancet Neurol.* 2010, Poulton J, et al *BMJ* 2009 338: 345, Rahman S and Poulton J, *Archives of Disease in Childhood* 2009 94: 3).

2. Scope

2.1 Aims and objectives of service

The rare mitochondrial disease service for adults and children aims to provide a comprehensive service for patients resident in the UK, this will include:

- a diagnostic service for children and adults with suspected respiratory chain disease in whom a diagnosis cannot be established on standard genetic tests available at regional genetic centres;
- a clinical service consisting of genetic counselling and clinical management for both inpatients and outpatients for adults and children with mitochondrial respiratory chain disease;
- clinical management advice for clinicians involved with patients with mitochondrial respiratory chain disease;
- specialist nursing input for advice, support and monitoring of quality of life issues and collaborative working with social services for community care;
- education opportunities for healthcare professionals locally and nationally;
- comprehensive information for patients and carers and the opportunity for patient involvement in strategic development of the service;
- national patient forum for education and information including national patient days;
- active and internationally-competitive research programmes; patient access for participation in research to develop new diagnostic techniques and clinical trials to improve the treatment of mitochondrial disease.

The service will be delivered through three established centres, each of which has an international reputation for clinical care and research in the field of mitochondrial disease. The main objective of the service is to improve the diagnosis and clinical care for patients with rare mitochondrial diseases.

Specific objectives of the service:

- accurate clinical and laboratory based diagnosis
- commence treatment where indicated
- genetic counselling
- prevent mitochondrial disease complications by multidisciplinary proactive care
- support to individuals and families
- risk determination based on family history or in association with laboratory test results
- accessible information (written and spoken) for families, other health professionals and patient support groups
- expert advice to other health professionals and commissioners

- training for clinicians and scientists who choose to specialise in mitochondrial disease
- education and training for other health professionals including those providing
- genetic counselling within other specialist services, and for undergraduate and post graduate students
- active participation in internationally-competitive research programmes and clinical audit
- equity of access through outreach model
- service development with patient and public involvement.

2.2 Service description/care pathway

The service will be delivered through three established centres, each of which has an international reputation for clinical care and research in the field of mitochondrial disease.

Newcastle

The Newcastle clinical service will be provided by a Consultant Paediatric Neurologist (paediatrics) and Consultant Neurologists (adults). The diagnostic service, led by a Consultant Clinical Scientist, will be fully integrated with the clinical service. The Newcastle centre (The Newcastle upon Tyne Hospitals NHS Foundation Trust) is also the main administrative centre for the Mitochondrial service with the local Consultant Clinical Scientist committing at least one day per week to ensuring coordination and communication between the three diagnostic centres.

London

The London clinical and diagnostic mitochondrial service, based at University College London Hospitals NHS Foundation Trust, is led by a Consultant Neurologist, holding weekly multi-disciplinary clinics providing a comprehensive diagnostic, treatment and management service for adults and children; a local Clinical Senior Lecturer in paediatric metabolic disease will coordinate paediatric care. The clinical lead will collaborate closely with the Head of Neurogenetics laboratory, the Clinical Director of Biochemical Medicine and Consultant Clinical Scientist and the Consultant Neuropathologist [muscle pathology] in order to provide all the diagnostic elements of the service.

Oxford

The local Consultant in Mitochondrial Genetics will run a multidisciplinary clinic and hold multidisciplinary meetings with clinicians and pathology monthly and with laboratory scientists every two weeks at Oxford University Hospitals NHS Trust. The clinical lead will provide a clinical liaison advisory service on mitochondrial genetics to the DNA laboratory at the Churchill Hospital. The head of the Oxford Radcliffe Hospitals NHS Trust Genetics Laboratory will lead the Churchill-based diagnostic service, whilst Honorary Consultant in Clinical Genetics will provide a diagnostic service focussed on

the biochemical and molecular analysis of patient-derived cell lines, as well as offering diagnostic advice by e-mail and telephone.All three centres see patients throughout England and Scotland, therefore the total patient access to clinical and diagnostic services is 57 million.

Diagnostic service

The three laboratory services in Newcastle, London and Oxford will provide a range of specialist histochemical, biochemical and molecular genetic tests, as part of established diagnostic algorithms, to provide an accurate and timely diagnosis of mitochondrial respiratory chain disease in referred samples. A number of these tests will be made available in more than one centre, to reflect referral patterns and numbers and enabling the provision of a back-up service, whilst other tests will only be available in one centre.

All three diagnostic centres are in regular contact, and the Newcastle Clinical scientist will lead to ensure that there are regular meetings and communication between the labs providing biochemical and molecular genetic testing.
Specifically, the three centres will provide expertise in the following areas in addition to the routine testing of common mitochondrial DNA mutations.

Newcastle:

1. tissue (muscle) histology and histochemistry
2. biochemical assessment of mitochondrial respiratory chain enzyme activities
3. assessment of mtDNA copy number in clinically-relevant tissues
4. comprehensive screening of mtDNA including mtDNA rearrangements and point mutations by whole genome sequencing
5. nuclear-mitochondrial gene screening (mtDNA maintenance disorders of adults and children; nuclear-encoded structural subunits of complex I).

London:

1. muscle histology and histochemistry
2. biochemical assessment of mitochondrial respiratory chain enzyme activities, including assessment of complex assembly and activity by Blue-Native Polyacrylamide Gel Electrophoresis (PAGE)
3. assessment of coenzyme Q10 in muscle and white blood cells
4. comprehensive screening of mtDNA including mtDNA rearrangements and point mutations by whole genome sequencing
5. nuclear-mitochondrial gene screening (mtDNA maintenance disorders of adults and children).

Oxford:

1. biochemical assessment of cytochrome oxidase and pyruvate dehydrogenase (PDH) activities in cultured skin fibroblasts
2. assessment of mtDNA copy number and dynamics in clinically-relevant tissues and patient cell lines
3. screening of mtDNA including mtDNA rearrangements
4. nuclear-mitochondrial gene screening (mtDNA maintenance disorders of adults and children; nuclear-encoded genes encoding cytochrome oxidase assembly factors).

All laboratories take part in available quality assurance (QA) schemes for molecular genetic testing. As no QA scheme is currently available for mitochondrial respiratory chain enzyme analysis, a “sample-swap” programme will be initiated between the three centres to ensure the quality of this service can be assessed.

Clinical service

The service is expected to deliver:

1. multidisciplinary clinics providing specialist care for all patients with rare mitochondrial diseases irrespective of age gender or ethnicity;
2. clear pathways of care for each patient including a focus on effective treatment of complications, prevention of potential complications and expert genetic counselling for families;
3. inpatient facilities for patients required specialised inpatient care for the management of complications.

Multidisciplinary clinics

All patients (both adults and children) should be seen in multidisciplinary clinics with access to physicians with proven expertise in the management of patients with complex mitochondrial problems. These clinics will be held on a weekly basis to provide timely care to patients. Patients will have access to specialised input from nurses, physiotherapists and speech therapists. Patients should have access to specialised medical services specifically: cardiologist, ophthalmologist, diabetologist, neurologist, geneticist and clinical scientists.

Patients with mitochondrial disease (and their families) often have major medico-social issues with many family members significantly disabled. Access to appropriate support is often confounded by a lack of professional awareness regarding mitochondrial disease. A range of psychological and social support services will be offered to meet the needs of patients and carers. These should be made available at the specialist centre and links to facilitate this at a local level should also be developed. The patients are managed by ensuring that there are close links between NHS England centre and local services, for example specific physiotherapy advice will be given in clinic but then managed locally after contact between our specialised physiotherapist and the local team. Diabetic care and management is through local services including the GP. The specific management plans for patients are documented in correspondence between clinicians and referring physician with copies to GP and patients. Follow up between NHS England centre and the patient is regularly done by the nurse specialist, including social care.

Pathways of care

Awareness and screening for potential complications is crucial in the management of patients with mitochondrial disease. Each patient should have a management plan for their specific mitochondrial disease with effective communication of that plan to patients and family members, as well as all health care professionals involved in the care of the patients. Guidelines for the management of patients are being established through the current NHS England service:

Rare mitochondrial diseases have very complex genetics – some patients have defects of the mitochondrial genome and others have involvement of the nuclear genome. Expert genetic counselling to discuss the risk of transmitting the genetic defect and the reproductive options available is crucial for individual patients and families. Women at risk of transmitting the mutation should be given the option of pre-natal or pre-implantation genetic diagnosis if appropriate.

The service must seek funding from the patients' local commissioners before pre-implantation genetic diagnosis treatment is commenced

Inpatient care
This should be available with specialised input as described above. Expertise in the management of acute aspects of mitochondrial diseases in both children and adults is crucial, e.g. management of status epilepticus and stroke-like episodes in adults. All invasive procedures such as skin or muscle biopsies will be performed either by a consultant or suitable specialist trainee directly supervised by a consultant.

Patient engagement and communications

The service is to:
1. work with NHS England to ensure considerations are given to communications;
2. provide an effective website for both patients and professionals;
3. the provider will organise regular patient information days.

Patient and carers' self-help and support groups are encouraged and all patients referred to a designated centre should be provided with relevant information about these groups. Patients, carers, GPs and referring clinicians should have access to a member of the clinical team for advice, information and support that is appropriate to the urgency of the needs of the patient.
The views of patients, carers and staff will be regularly and formally sought and the results openly available.Patient engagement, feedback and support should be actively encouraged. The service should seek to support patients as innovatively as possible in light of there not being an active patient support group.

The Mitochondrial Service website (http://www.mitochondrialncg.nhs.uk/) continues to be hosted by the Newcastle upon Tyne Hospitals NHS Foundation Trust, providing information to both patients and professionals regarding:
- clinical presentation
- diagnosis
- treatment
- clinical management of mitochondrial disease
- out of hours medical advice for professionals
- a designated telephone helpline will be available, supervised by the specialist nurse to provide information and support.

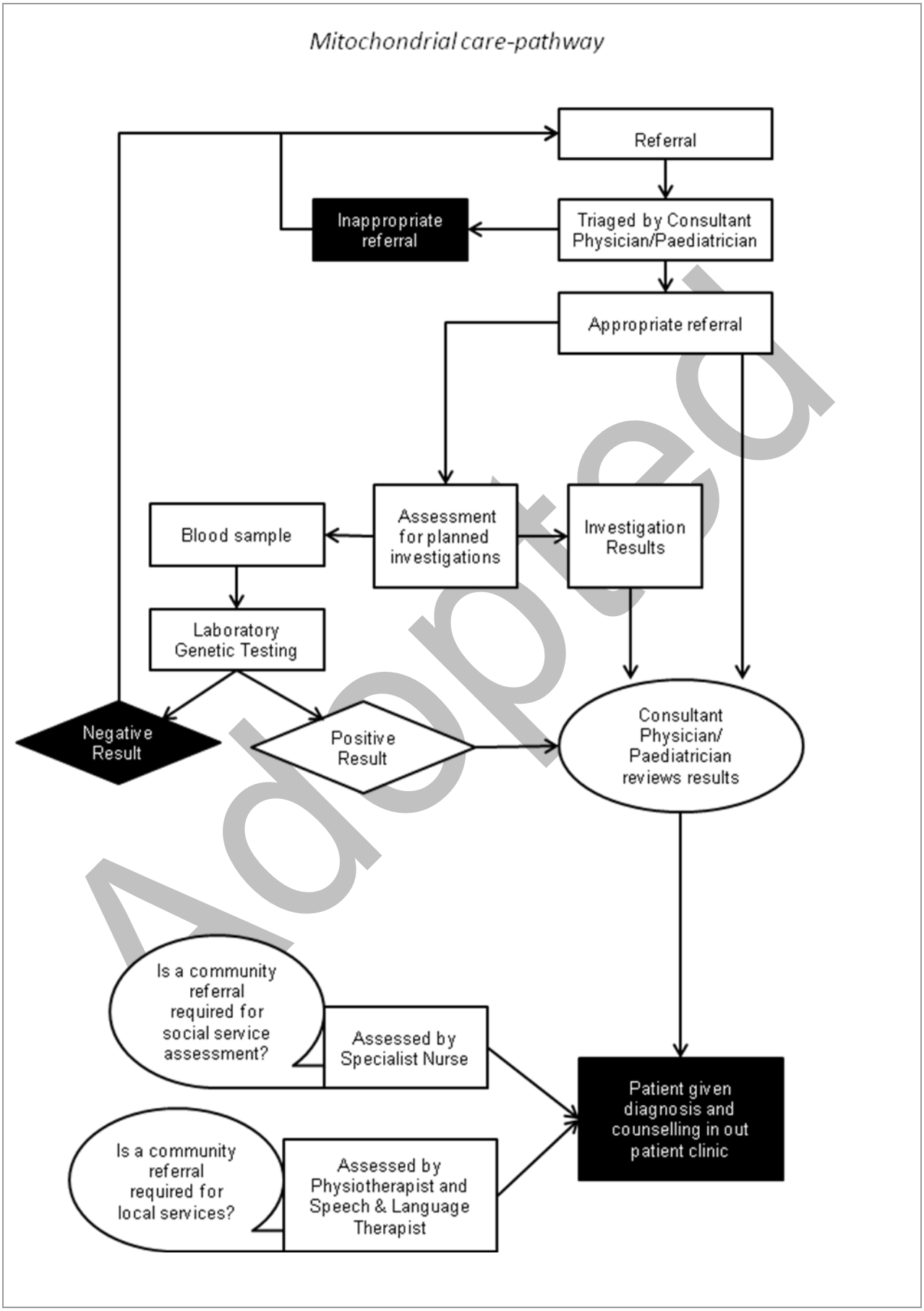
Research
Whilst NHS England does not commission research, teams are expected to actively

participate in research to continuously improve services**.**

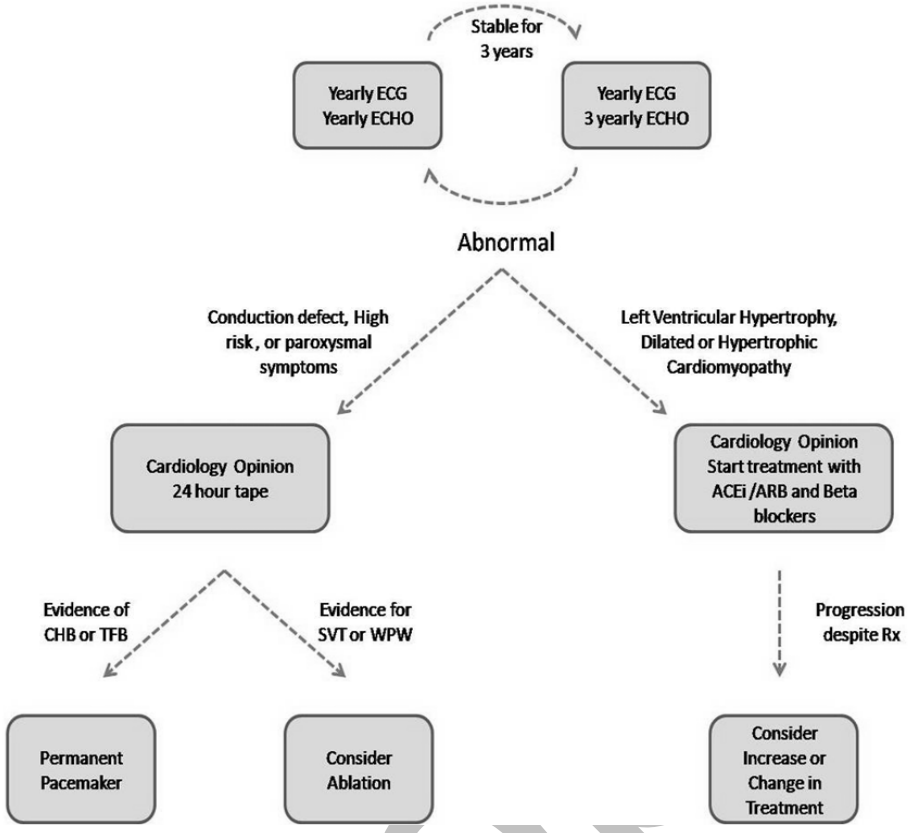
The service is expected to deliver:

1. research which will directly improve the quality of life and management of patient with rare mitochondrial diseases including inclusion in clinical trials
2. research which is funded by National or international funding agencies such as Medical Research Council (MRC), Wellcome Trust or National Institute for Health Research (NIHR) to ensure high quality of research.

The centre has a strategy which documents current and planned research activity, the resources needed to support activity and objectives for development.

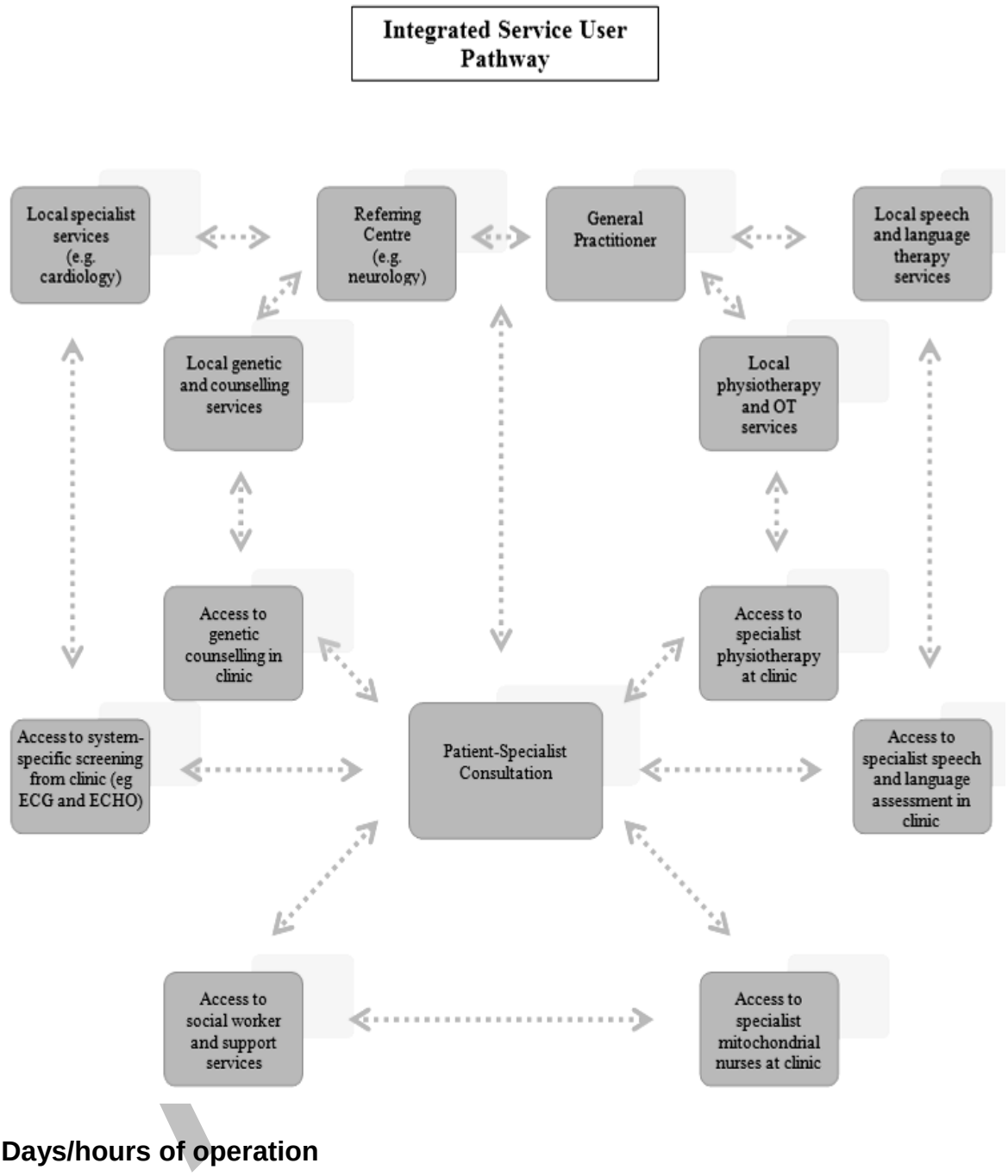


Mitochondrial Disease: Cardiology Guidance



Key:

ACEi	angiotensin converting enzyme inhibitor
ARB	angiotensin II receptor blocker
CHB	complete heart block
TFB	trifascicular block
SVT	supra-ventricular tachycardia
WPW	Wolff-Parkinson-White syndrome



Days/hours of operation

The clinical service is available on an on call basis to cover for emergencies, with more routine requests and clinics provided 0700-1800 hours week days.
The laboratories work standard hours but for urgent samples evening and weekend cover is provided.

2.3 Population covered

All providers of the service have a duty to co-operate with the commissioner in

undertaking Equality Impact Assessments as a requirement of race, gender, sexual orientation, religion and disability equality legislation. Rare mitochondrial diseases

Affect patients of all races although there are specific genetic implications for women who carry mitochondrial deoxyribonucleic acid (DNA) mutations. All issues will be monitored locally by the providers and NHS England.

2.4 Any acceptance and exclusion criteria

Criteria:

- for the service there is an established referral pattern with user manual and referral details and forms available on website http://www.mitochondrialncg.nhs.uk/
- all diagnostic referrals are triaged by the Laboratory Head or Consultant Clinical Scientist at each centre
- all clinical referrals are triaged by the lead clinician.

Routes:

- GP and self-referrals from families with known molecular diagnoses
- suspected and proven rare mitochondrial disease from consultant physicians throughout England and Scotland.

Exclusion criteria

All diagnostic samples and clinical referrals are triaged by senior scientists or clinician. Exclusion is only if the likelihood of the patient having a rare mitochondrial disease is minimal or more appropriate tests or services are available locally.
An example of a specific exclusion is that patients with symptoms of chronic fatigue or other non-specific features should be seen by a neurologist or appropriate physician and only referred if appropriate, to NHS England service.

Pre-natal genetic diagnosis is not funded by the National designation funding.

Response time & detail and prioritisation

All clinical referrals are triaged following the 18 week referral to treatment (RTT) pathway

The laboratories aim to meet White Paper targets for standard referrals. In Newcastle and London, testing of large genes (e.g. whole mitochondrial genome sequencing – 36 exons; full *POLG1* gene analysis – 22 coding exons) is reported between 8-10 weeks. In Oxford, biochemical and genetic testing of **cytochrome oxidase** (COX) and pyruvate dehydrogenase (PDH) (and related genes) is reported between 2-5 weeks, and genetic testing of mitochondrial DNA maintenance genes (e.g. full *POLG1* gene analysis) is reported in approximately 12 weeks. At all centres, urgent samples can be processed and reported quickly should this be requested to aid clinical decisions.

Discharge criteria

Patients for which the investigations and the clinical examination exclude a possible diagnosis of mitochondrial disease or are diagnosed with an alternative or acquired condition are discharged from the service. Diagnosed patients are transferred to local care services where appropriate with a detailed management plan**.** All discharge planning will be managed by the multi-disciplinary team in charge of the case with local health and social care providers being fully informed of the patient's condition and any responsibilities they will have to assume. This will be formalised in written communication to the patient's GP and all other relevant parties.

2.5 Interdependencies with other services

3. Applicable Service Standards

3.1 Applicable national standards e.g. NICE, Royal College

The nationally designated Rare Mitochondrial Service providers must be fully integrated into their trust's corporate and clinical governance arrangements and must fully comply fully with Clinical Negligence Scheme for Trusts (CNST) and Care Quality Commission (CQC) requirements in terms of quality and governance. The hub centres are responsible for overseeing the governance arrangement of any spoke clinic provided under sub-contractual arrangements.

Each centre will ensure that there are:

- regular meetings with patient representatives;
- all practitioners will participate in continuous professional development and networking;
- patient outcome data is recorded and audited across the service.

The commissioners and service will conduct a formal Joint Service Review at least every six months. All centres must participate in the national audit commissioned by NHS England - audit meetings should address:

- clinical performance and outcome
- process-related indicators, e.g. efficiency of the assessment process, prescribing policy, bed provision and occupancy, outpatient follow up etc.
- stakeholder satisfaction including feedback from patients, their families, referring surgeon and General Practitioners.

See also NHS England Service Standards for Rare Mitochondrial Disorders of Children and Adults

4. Key service outcomes

Quality Performance Indicator	Threshold	Method of measurement	Consequence of breach	Report Due
Patient experience	>80% satisfied or better	Patient questionnaire	Review by local team and by national tripartite NHS CB centre meetings	Twice per year
Patient safety	<5% muscle biopsy complications	Audit of muscle biopsy	Review by local team and by national tripartite NHS CB centre meetings	Twice per year
Patient outcomes	>80% patients confirmed or excluded as having mitochondrial disease on basis of clinical and or biochemical and or genetic criteria	Audit of all cases seen in the service	Review by local team and by national tripartite NHS CB centre meetings	Twice per year

5. Location of provider premises

Oxford University Hospitals NHS Trust
The Newcastle upon Tyne Hospitals NHS Foundation Trust
University College London Hospitals NHS Foundation Trust