**D04/S(HSS)/a**

**2013/14 NHS STANDARD CONTRACT**
**FOR DIAGNOSTIC SERVICE FOR RARE NEUROMUSCULAR DISORDERS (ALL AGES)**

**PARTICULARS, SCHEDULE 2 – THE SERVICES, A - SERVICE SPECIFICATIONS**

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| **Service Specification No.** | D04/S(HSS)/a |
| **Service** | Diagnostic service for rare neuromuscular disorders (All Ages) |
| **Commissioner Lead** | |
| **Provider Lead** | |
| **Period** | 12 months |
| **Date of Review** | |



## 1. Population Needs

### 1.1 National/local context and evidence base

**Limb-girdle muscular dystrophy**

Limb girdle muscular dystrophies (LGMDs), Emery-Derifuss muscular dystrophies (EDMDs) and Myofibrillar (MFMs) are clinically and genetically heterogeneous disorders that can be distinguished by clinical history, clinical examination, clinical investigations, muscle biopsy and genetic testing. Presentation (ranging from early childhood to late adult life), disease severity, inheritance and potential complications are highly variable depending on the condition subtype considered. The diagnosis of a condition subtype without further qualification is therefore inadequate and the definition of the specific subtypes carries with it important information. At the moment no specific cures are available for any of the subtypes of LGMD, EDMD or MFM, however precise diagnosis offers the potential for the provision of accurate genetic counselling and of appropriate management of disabilities and complications, such as cardiac and respiratory. Furthermore, future therapies (currently in the preliminary stages of clinical trials) will require precise knowledge of the exact gene defect. Noteworthy, EDMD represent the most common form of muscular dystrophy after Duchenne and Becker and associates with a high risk of sudden cardiac death. In view of this, diagnosis and prompt management of these conditions and their cardiac complication is pivotal.

These rare inherited neuromuscular conditions mainly cause weakness and wasting of pelvic and shoulder girdle muscles initially, which could progresses to involve all muscles. In MFM, distal muscle weakness is most common and more pronounced than proximal weakness. The progressive weakness can ultimately lead to the inability to walk independently at some stage of their disease, though the age at which this occurs is highly variable from patient to patient and condition. Cardiac involvement is commonly observed in specific subtypes of LGMDs (i.e. LGMD2I), MFMs (i.e. desminopathy), and in particular it represent a frequent manifestation of EDMD, where cardiac involvement is a common complication usually occurring after the second decade. EDMD is also characterized by joint contractures that usually appear during the first two decades, followed by muscle weakness and wasting. Specific subtype of LGMDs, EDMDs and MFMs are also characterized by rare associated clinical features, such as peripheral neuropathy and cataract in MFMs.

The heterogeneity of the group is the main reason for the complexity of diagnosis. Diagnosing the various disorders requires information from the clinical presentation and the results of various investigations, such as serum creatine kinase (CK), muscle biopsy and genetic testing. This may involve the analysis of a large number of individual exons as very few recurrent mutations in these genes have been identified. Despite the overall "LGMD" or "MFM" designation implying a predominant clinical presentation or muscle involvement, there may be considerable clinical heterogeneity and different management issues. Moreover, as there are many new dominant mutations, a high level of diagnostic suspicion needs to be maintained, even without a clear family history.

There are at least 22 different LGMDs, seven inherited dominantly and the rest recessive. The most common form of EDMD is dominantly inherited, but recessive and X-linked forms are as well recognized. MFMs are mostly dominant and mutations in at least six genes have been recognized so far. Allelic heterogeneity is responsible for heterogeneous phenotypes and mutations in the same gene could account for different clinical conditions, such as in the case of LGMD1A caused by mutations in the MYOT gene and allelic to one subtype of MFM. About 25% of LGMDs, and 50% of MFMs or EDMDs result negative to mutations in all the known genes indicating further genetic complexity for these conditions.

**Congenital muscular dystrophy and myopathy**

The term congenital muscular dystrophy (CMD) and congenital myopathies (CMY) refers to conditions characterised by:

- Weakness, hypotonia, contractures
- onset at birth or within the first year of life and
- pathological changes on the muscle biopsy indicating a primary muscle involvement.

This is to differentiate them from congenital conditions in which muscle weakness is secondary to neurogenic conditions (neuropathies, or motor neuron diseases). Mental retardation with associated structural brain changes can also be present in a

proportion of CMD cases but is not usually present in CMY.

From a clinical perspective there is extreme variability of clinical severity of both CMD and CMYs, some children having severe muscle weakness and respiratory insufficiency at birth or shortly after, and typically not surviving beyond the first few weeks or months of life; to much less severe variants in which acquisition of motor milestones such as walking independently is often delayed, but possible, and survival into adult life is expected.

From a histopathological perspective, the main difference between CMD and CMY is the presence of signs of degeneration and regeneration in the CMDs; and of structural muscle defects on detailed histochemical and electron microscopic examination in CMY. While this distinction allowed in the 1950's and 60's to recognize the first CMDs syndromes on one end, and the structural CMYs at the other end, recent genetic advances has clearly indicated a substantial clinico-pathological overlap between these two groups of conditions. In the last decade it has been shown for example that individual gene defects can give rise to muscle histopathological changes that can lead to either a diagnosis of CMD or of CMY, depending on the age at which muscle biopsy is obtained, and/or which muscle is biopsied. Typical relevant examples are mutations in SEPN1 (responsible both for a form of CMD, RSMD1 (Rigid Spine Muscular Dystrophy 1), and for a form of CMY, multiminicore disease), in Ryanodine receptor 1 (RYR1) (typical involved in Central Core disease, but with severe dystrophic variants now been well described), in DYNM2 (as in RYR1), and in COLVI, typically mutated in Ullrich CMD, but also associated with congenital fibre type disproportion, considered a congenital myopathy. The phenotypes of patients having mutations in- for example, Selenoprotein N (SEPN1) and pathological features of CMD or CMY are identical.

Most of CMDs and several of the CMYs are inherited as autosomal recessive conditions; one of the CMD variants and several of the CMY variants can be due to de-novo dominant autosomal gene defects. One of the CMY is X-linked recessively inherited.

While curative treatment is currently not available for any of the CMD or CMY forms, the identification of the precise disease subtype offers the opportunity to provide the family with accurate prognosis and genetic counselling. As specific complications (such as respiratory failure; failure to thrive; scoliosis; progressive limb contractures) occur in some CMD and CMY syndromes but not in others, a precise diagnosis will help the management and supportive treatment of these conditions.

In view of the clinical and genetic heterogeneity of these disorders, the diagnostic process invariably involves a detailed clinical examination; electrophysiological studies; brain imaging; muscle biopsy; genetic studies, muscle imaging. These latter studies are typically focused on the relevant gene, following a rational diagnostic flowchart.

**Congenital myasthenic syndromes**

Congenital Myasthenic Syndromes (CMS) are a rare group of heterogeneous

disorders affecting all ages and gender. It is estimated that there are 300 patients

affected by the condition in the UK although there are likely more undiagnosed patients who have an incorrect diagnostic label or are mildly affected or asymptomatic. The main clinical feature is that of fatigueable muscle weakness which is variable in severity between patients and can change within the same patient – either progressing or improving through the course of their life. Some patients have respiratory or bulbar muscle involvement and for a number the condition is life-threatening. There are nine genes screened for in the CPA accredited laboratory and a further three that can be screened within the research laboratory where appropriate. About 40% of CMS patients do not currently have an identified gene mutation but with the discovery of new genes this is reducing.

Unlike many genetic conditions, CMS symptomatic treatments can produce marked improvements. The treatment in those correctly diagnosed can lead to marked improvement in quality of life with normal life spans. Of note, the treatments need to be individualised to the specific genetic mutations because beneficial treatments for one CMS subtype can cause worsening in others. Additionally as the immune system is not involved in CMS there is no role for immunosuppressive drugs or thymectomy as is frequently used in the commoner autoimmune myasthenia gravis. By attaining an accurate genetic diagnosis CMS patients will avoid undergoing unnecessary or potentially harmful treatments, which has been the case for many of our older patients.

**Muscle channelopathies**

Patients with muscle genetic channelopathies experience debilitating episodes of muscle paralysis [periodic paralysis] and or episodes of severe muscle stiffness [myotonia or paramyotonia]. Many patients develop significant disabling permanent muscle weakness over time. For example 40% of patients with periodic paralysis need walking aids or wheel chairs because of muscle weakness by mid-30's. Importantly there are treatments (e.g. carbonic anydrase inhibitors or mexilitine) which can aid symptoms significantly and therefore an early an accurate genetic and clinical diagnosis is essential. Diagnosis may often be delayed because of the rarity of the conditions and the lack of widespread expertise. NHS England (NHSE) channelopathy service provides a full clinical assessment service (one stop same day patient assessment, detailed specialised neurophysiology and genetic testing) and also a genetic diagnostic service (clinicians from around England can refer deoxyribonucleic acid (DNA) samples to the service).

Muscle channelopathies include periodic paralysis and myotonia congenita. Patients with periodic paralysis have a life-long tendency to develop attacks of muscle weakness often brought on by exertion. In its most severe form there is total body paralysis which may last days. In myotonia congenita patients experience permanent muscle stiffness which can be severe and limit normal daily activities. Accurate diagnosis is difficult and affected patients often experience a long delay of years before a correct diagnosis is achieved and effective treatment instituted. Unfortunately patients are often misdiagnosed and sometimes the variable severity and intermittent nature of some of the symptoms leads to the erroneous suggestion

the symptoms are psychological.

Specialist clinical, electrophysiological and molecular genetic assessment is required to make an accurate diagnosis. The clinical service at the University College London Hospitals NHS Foundation Trust offers a one stop-same day assessment in which patients are evaluated clinically and then undergo detailed electrophysiological testing in collaboration with a consultant neurophysiologist. With informed consent patients are then offered detailed genetic testing to achieve a DNA-based diagnosis in the DNA laboratory. Patients are followed up to receive genetic counselling and treatment. Effective medications are available in accurately diagnosed patients and often significantly improve quality of life.

**Evidence base**

The limb-girdle muscular dystrophies (LGMD)
The LGMD, MFM and EDMD are individually very rare conditions, and although there is no cumulative prevalence data, point prevalence of LGMDs in the Northern England population is 2.27/100.000 (Norwood et al., 2009). No evidence based guidelines exist to date on the management of these conditions, but experts from Newcastle and other European countries are leading collaborative task forces for the development of guidelines for the best practice management (Norwood et al., 2007). With the identification of novel genes and mutations the ability to achieve diagnosis in this group of condition has increased, and the clinical characterization of each subtype is constantly improving. Risks of important complications, such as cardiac and respiratory compromise, and their management can be addressed much more specifically, improving quality of life and longevity of these patients, as also addressed in several publications from NHS England service team (Norwood et al., 2007; Bushby et al. 2009, Hicks et al; in press; Klinge et al, in press; Aboumousa et al, 2009). For example, identification of a LMNA gene mutation should indicate aggressive treatment with implantable defibrillator (Meune et al., 2006). Clinical and genetic heterogeneity of these conditions increases the complexity not only of clinical management but also of genetic counselling.

Research is part of the clinical practice and the output of the service is world class with several directly relevant publications, many of which in the leading specialty journals. Over the last year, the service team have collaborated in the completion of important clinical and care guidelines, for professionals (care standards for Duchenne and SMA) and/or patients (clinical factsheets for subtypes of LGMDs, MFM and BM), as well as in the promotion of knowledge in the field of neuromuscular diseases. Efforts were also made towards identification of novel causative genes in undiagnosed patients. A recent research led to the identification of mutations in a novel gene, ANO5, in about 25% of undiagnosed LGMD patients (Hicks et al, in press). Moreover, a rare mutation in the novel BAG3 gene has been identified in a severe form of MFM (Ogderel, et al., 2010).

The diagnostic role of the service has also a pivotal role in the future enrolment of patients in patients' registries and future trials, as also outlined in an international workshop on patient registries for rare, inherited muscular disorders (Sarkozy et al., 2008).

## Congenital muscular dystrophies and myopathies

Over the last 10 years there have been major developments in our understanding of the biochemical basis, genetic mechanisms and natural history of the congenital muscular dystrophies and myopathies. This data has been reviewed in regular European Neuromuscular Centre (ENMC) and International workshops and meetings, with major contributions from Professor Francesco Muntoni, Professor Caroline Sewry and colleagues including Dr Stephanie Robb, Dr Cecilia Jimenez and Dr Lucy Feng. Research in the centre and in collaboration with colleagues internationally has enabled identification of the genetic basis of many CMD subtypes, thus enabling accurate diagnosis, prognosis and genetic counselling. Natural history data on the largest series of children with MDC1A, Ullrich and SEPN1 CMD subtypes have been collated, clarifying prognosis and the incidence of complications, many of which, including scoliosis and respiratory failure can be prospectively monitored and treated, with significant reduction in morbidity and mortality. For example, before the advent of non-invasive ventilation (NIV), most children with CMD and many with CMY died from respiratory failure in childhood or required prolonged periods of care in intensive care units because of the unexpected respiratory complications.

By applying anticipatory care, monitoring disease specific complications with careful respiratory surveillance, management of feeding difficulties and failure to thrive, improved postural management including spinal and orthopaedic surgery and timely introduction of NIV, most of the children referred to service can be transitioned to adult services

## Congenital myasthenic syndromes (CMS)

No public health data regarding the prevalence of congenital myasthenic syndromes is available. However, they are an extremely rare group of mainly recessively inherited neuromuscular disorders. In 2007 a study of referrals to the service found the UK population prevalence of genetically confirmed cases to be 2.2 per million1. The total number of cases is likely higher due to misdiagnosis and some people having no or minimal symptoms. For instance, although a genetic disorder, in some cases onset is in adulthood.

By virtue of its rarity, randomised control trails (RCTs) are not an option in CMS. There are a number of publications about the use of drug treatments in CMS such as pyridostigmine, 3, 4-Diaminopyridine, ephedrine, and fluoxetine some of which were conducted in Oxford,[2,3,4,5,6,7]. The use of these drugs has been supported or indeed pioneered by showing a molecular basis for altered neuromuscular transmission.

There are very few other centres in the world with expertise in CMS.

## Muscle channelopathies

The muscle channelopathies are individually very rare conditions, and although there is no cumulative prevalence data, point prevalence our estimates based on data

collection in England over the last 10 years is 2-3/100000. No evidence based guidelines exist to date on the management of these conditions, but experts from the UK ,USA and European countries are leading efforts for development of guidelines for the best practice management. There is some evidence that certain treatments are effective in these disorders and it is therefore essential to make an accurate genetic diagnosis as early as possible. Carbonic anhydrase inhibitors reduce the frequency of attacks in periodic paralysis and mexiletine reduces the severity of muscle stiffness in patients with myotonia and paramyotonia. Importantly recent research indicates that the development of severe muscle weakness and severe permanent disability relates to progressive water accumulation in muscle and furthermore that new sensitive MRI techniques may be the best way to monitor this and treatments should be adjusted on the basis of MRI water content not only clinical symptoms. New MRI techniques are being actively researched to determine the best method to monitor patient and treatment response. The work of the Queen Square NHS England group collating and the related research group has been at the forefront of developing the international evidence base for best practice in diagnostics [DNA and Electrophysiology] and patient management over the past 10 years- see example recent publications below.

## 2. Scope

### 2.1 Aims and objectives of service

The service establishes a national network of specialist services offering an integrated clinical and investigative diagnostic and advisory service for patients with specified forms of rare inherited neuromuscular diseases: the limb-girdle muscular dystrophies, congenital muscular dystrophies and myopathies, congenital myasthenic syndromes and ion channel disorders of muscle. The network enables all patients with these disorders access to specialised diagnosis and advice on management and treatment. All of these disorders are individually rare, usually progressive and always disabling conditions of skeletal muscle. Many of the problems in diagnosis in these groups are to a certain extent shared as they largely relate to their heterogeneity and the rarity of the individual diseases. The expertise to deal with the diagnosis and implications of these different disorders has developed in individual centres, as listed below, all internationally recognised for their work in these fields. The work is therefore distributed between the groups, with analysis for specific diseases taking place in designated centres:

The aim of the service is to make a precise molecular or clinical diagnosis in patients with rare neuromuscular conditions, and to assess fully the extent of their disease.

**The limb-girdle muscular dystrophies** (Newcastle)
**The congenital muscular dystrophies and myopathies** (London – Dubowitz Neuromuscular Centre)
**The congenital myasthenic syndromes** (Oxford)
**The muscle channelopathies** (London – Institute of Neurology)

The definitive diagnosis for a patient is resolved by identifying the primary gene defect. Each of those groups of disorders is highly heterogeneous and this heterogeneity and the resultant complexity of diagnosis has been a key feature in seeking and achieving designation of the service as a national resource. Each condition involves multiple genes and each centre uses a specific battery of techniques to focus the search for DNA mutations. Because of the subtle differences in the diagnostic approach to these disorders, each is dealt with separately in this document. Overall, the focusing process may include specialised clinical assessments, neurophysiological tests, or immunological analyses on tissue biopsies, according to the disease group. It is the multidisciplinary nature of this process that separates NHS England service from other, purely genetic, resources.

Over the last twenty years, the ability to make a specific diagnosis for patients with these types of rare muscle disease has improved dramatically. These enhanced molecular genetic and protein diagnostics provide the potential to offer patients and their families improved management, prognostic information and access to precise genetic counselling. As these developments have arisen directly out of research findings, expertise in these areas has been concentrated in groups with a research interest in the problem.

These disorders are individually rare, and a central concentration of expertise is necessary to offer a national service, provided there is equality of access. Failure to designate this as a national service would have led to inequality of access and suboptimal management. Offering a truly national service has removed these barriers to inequality of service thereby offering all patients the ability to access the most advanced diagnostic services and obtain the best possible information on which to base their future life and reproductive decisions. Although patients will be responsible for travelling to the specific centre, all the subsequent services are nationally funded and free of charge if they live in England and Scotland. We are able to accept patients, biopsies and DNA samples from outside these regions, but charges will have to be made.

**Specific aims and overview**

**Limb-girdle muscular dystrophies**

The service aims to improve the diagnosis and management of LGMD. People with a suspected diagnosis of LGMD can be seen or have muscle or DNA sent for analysis here. Different levels of service can be provided according to the needs of the patient and his referring clinician, but the basic levels of NHS England referral are:

1. in the first option, a patient may be admitted to Newcastle upon Tyne Hospitals NHS Foundation Trust for specialised clinical investigations, removal of a muscle biopsy and subsequent immunoanalysis, and gene mutation analysis
2. in the second option the patient attends as an outpatient only, protein analysis is undertaken on a previously stored biopsy, and DNA analysis is performed
3. in the third option, the patient doesn't travel to the referral centre. Protein analysis is undertaken using a frozen muscle biopsy taken previously somewhere else and stored, and these investigations guide and focus subsequent genetic analysis on DNA from a blood sample. Unfortunately, it is

often not possible to undertake DNA analysis alone for the LGMDs, without protein analysis, because the number of possible genes for study is so large. However with good clinical and ancillary information, we offer DNA testing in certain situations without previous biopsy, for example when no biopsy is available and the patient will not consent to this investigation or when the protein analysis for a particular condition is non-informative.

Based on the precise diagnosis and clinical assessment, for patients who are seen at Newcastle upon Tyne Hospitals NHS Foundation Trust, specific advice on physiotherapy and other aspects of day to day support as well as genetic counselling will be provided. For patients not seen in Newcastle, the information will be provided for local physicians and other professionals to provide appropriate follow up.

In the Newcastle service the target population is characterized by a phenotype with features specific for one of the following inherited neuromuscular conditions, independently by the genetic basis and inheritance: Limb girdle muscular dystrophy (LGMDs), Emery Dreifuss muscular dystrophy (EDMD), myofibrillar myopathy (MFM), including rare conditions overlapping with LGMDs, EDMDs or MFMs, such as Bethlem myopathy (BM) or congenital myasthenic syndromes with an LGMD phenotype.

Patients with a clinical diagnosis of Becker muscular dystrophy (BMD) without dystrophin mutation are also included as BMD widely overlaps with the above mentioned conditions and patients with some form of LGMDs (such as LGMD2I) or rare overlapping conditions such as FHL1-related myopathies are often misdiagnosed as BMD with major implications in terms of genetic counselling and clinical management for the patients and their families. Clinical pictures not covered by the service are those that do not belong to those above mentioned, in particular acquired conditions, and if a diagnosis of LGMD, EDMD, MFM or any other rare overlapping conditions is excluded, the patient is discharged from the service. It is important to note that there are additional as yet unrecognised forms of LGMD that at present cannot be diagnosed. This accounts for at least 25% of a well-defined clinical population (add our references if we are allowed to). However, the service offers advanced multidisciplinary management also for those patients for whom a definite genetic diagnosis is not achieved. Moreover, a follow up is offered to all undiagnosed patients and clinic notes and investigations are reviewed in order to screen novel genes identified in the meanwhile.

**Congenital muscular dystrophies and myopathies**

The service provides a specialised diagnostic and advisory service for patients with suspected congenital muscular dystrophy (CMD) or congenital myopathy (CMY).

The service aims to improve the diagnosis of CMD and CMY and to support local medical teams and families in managing these complex conditions.

Patients are reviewed in the service in two streams:

**Level 1** – Muscle and skin biopsy analysis/Genetic study only

Patients are not assessed in person, but histological, histochemical, immunohistochemical and electron microscopy studies or review of stained slides from a previously obtained muscle biopsy are performed and a detailed biopsy report is produced based on this information. The biopsy analysis results are reviewed with the patient's clinical history and results of other investigations at a weekly multidisciplinary meeting. A summary letter from a consultant is forwarded with the report to the referring clinician in each case. These pathology investigations may serve as a guide for subsequent CMD or CMY genetic investigations or may exclude these disorders.

Genetic analysis is performed on patient blood DNA samples and Ribonucleic acid (RNA) samples extracted from muscle or skin fibroblasts for the known genes responsible for CMD and CMY. Confirmation of the diagnosis at the genetic level helps not only accurate prognosis, long term anticipatory care and management but also genetic counselling for the conditions.

**Level 2** – Comprehensive assessment

The patient attends Great Ormond Street Hospital for Children NHS Foundation Trust and will be clinically assessed by a team including paediatric neurologist, specialist neuromuscular physiotherapist, speech and language therapist, orthotist, dietician and neurophysiologist. They will receive a full diagnostic analysis including muscle imaging, brain imaging (if indicated), muscle biopsy and genetic study.

Muscle imaging in the form of muscle ultrasound and or muscle magnetic resonance imaging (MRI) is also performed when necessary, and the results discussed at the regular combined neuroradiology meetings. A detailed report is produced and the patient and family will receive counselling about the condition and on-going care. This service is available both to patients without a final diagnosis; and to patients in whom a final diagnosis has already been established, but when an individualised and appropriate multidisciplinary management plan is required.

New patients to the service can be reviewed for on-going diagnostic and management issues, if appropriate. In case the patient is followed up for a period exceeding one year from the original referral, the patient will be considered as a tertiary referral under clinical commissioning groups' agreement.

Collation of clinical, laboratory and follow up data on patients referred to the service has resulted in the publication of seminal papers on the natural history of these rare conditions and allowed evidence based guidelines to be made regarding internationally recommended standards of care. Novel diagnostic tests have been devised; novel genes responsible for these variants identified, as novel genotype-phenotype correlations which have expanded considerably the border of previously described entities. Outcome data gathered from the service will also form the basis of clinical trials for future therapies in these conditions. The clinical and laboratory services are closely linked to the neuromuscular research group at University

College London Institute of Child Health, lead by Professor Francesco Muntoni. This group has a major focus on CMD and CMY, investigating the clinical, biochemical and genetic basis of these disorders. The group identified several of the genes for CMD and has published extensively on genotype phenotype correlations in CMD and CMY. Professor Muntoni and his group frequently lecture at national and international meetings on CMD, CMY and other neuromuscular conditions. The service provides teaching and training in the diagnosis and management of neuromuscular disorders for postgraduate trainees from the UK and abroad. The group organises a yearly international advanced neuromuscular course.

**Congenital myasthenic syndromes**

There is a national outpatient and an inpatient service for congenital myasthenic syndrome (CMS) patients commissioned by NHS England separately funded. This service will encompass all aspects of diagnosis and treatment utilizing the specialist clinical, neurophysiology and molecular genetic skills available in Oxford.

The service offers access to specialist clinical neurology assessment including specialist adult neurologist, specialist paediatric neurologist, clinical CMS fellow, specialist physiotherapist and molecular genetics expertise.

There is access to neurophysiologists experienced in myasthenia assessment, one of whom specialises in paediatrics.

The service has access to rapid genetic screening and functional screening on new mutations that are identified allowing rapid translation of cutting edge research into clinical practice.

Inpatient assessment for investigation and treatment is not funded by NHSE but in addition is offered. The service also has a phone helpline for patients and carers.

**Muscle channelopathies - the conditions and the service**

Patients with muscle genetic channelopathies experience debilitating episodes of muscle paralysis [periodic paralysis] and or episodes of severe muscle stiffness [myotonia or paramyotonia]. Many patients develop significant disabling permanent muscle weakness over time. For example 40% of patients with periodic paralysis need walking aids or wheel chairs because of muscle weakness by mid-30's. Importantly there are treatments (e.g. carbonic anydrase inhibitors or mexilitine) which can aid symptoms significantly and therefore an early an accurate genetic and clinical diagnosis is essential. Diagnosis may often be delayed because of the rarity of the conditions and the lack of widespread expertise. NHS England channelopathy service provides a full clinical assessment service (one stop same day patient assessment, detailed specialised neurophysiology and genetic testing) and also a genetic diagnostic service (clinicians from around England can refer DNA samples to the service). At the National Hospital for Neurology and Neurosurgery, which is part of University College London Hospitals NHS trust, colleagues offer a comprehensive diagnostic and advisory service to patients with a group of neuromuscular disorders

known as the skeletal muscle channelopathies. These disorders include conditions such as periodic paralyses [in which patients have episodes of total or partial muscle paralysis] and inherited myotonias [in which patients experience persistent, often disabling muscle stiffness]. All these conditions are treatable but achieving an accurate diagnosis is complex. A precise diagnosis depends on a coordinated approach which begins with a detailed clinical assessment and often also involves specialised neurophysiological assessment and DNA analysis. An accurate diagnosis is important since this not only allows precise genetic counselling but will also result in the institution of effective treatment. It is common that many patients with these disorders are mis-diagnosed and we therefore encourage clinicians from all over the UK to refer patients whenever this diagnostic possibility is considered. Effective treatment will significantly improve quality of life for these patients. Furthermore, patients with periodic paralysis are less likely to develop permanent disabling muscle weakness if early treatment is given.

**Key elements of the national muscle channelopathy diagnostic and advisory service**

- clinical assessment
- neurophysiological assessment
- DNA analysis.

**Beneficial outcomes for patients:**

- accurate diagnosis achieved
- genetic counselling
- effective treatment initiated
- prevention of muscle weakness
- exclusion of diagnosis.

**2.2 Service description/care pathway**

**Service description**

**Limb-girdle muscular dystrophies**

Based on past referral patterns, the majority of referrals are likely to come via consultant neurologists, and neuropathologists. As some of these patients will have been discharged by specialists services a proportion of referrals are also likely via the GP. Referrals to the service will be via a pre-referral proforma or clinical letters.

Levels of service are described in section 1.1. Details of muscle biopsy analysis and genetic analysis are specified in Appendix 1.

**Clinical service**

The clinical appointment is offered to patients referred because of a personal of familial history of neuromuscular condition, with a likely genetic basis, and

phenotypically suggestive for LGMD or other overlapping conditions. Patients with alternative diagnosis are forwarded to the competent services or relative NHS England service if available. When the appointment is arranged, an information letter is sent to the patient.

The NHS England clinic service is a multidisciplinary clinic and the patient will undergo a comprehensive assessment for specialised diagnosis and advice that is structured as follows:

- full clinical assessment by the consultant expert in rare neuromuscular disorders
- muscle assessment by the physiotherapist expert in rare neuromuscular disorders
- respiratory assessment with forced vital capacity measurement in sitting and lying
- advice about available clinical, physiotherapic and orthotic treatment and management
- genetic counselling by a neuromuscular specialist nurse
- advice about social care, independent living, benefits, etc. by the regional care advisor
- arrangement of biopsy and/or DNA analysis. Details are described in appendix 1
- a summary clinic letter is issued by the leading consultant after each clinic appointment and sent to the patient as well as all medical professionals identified by them or others as important to their on-going care
- a Newcastle Muscle team contact sheet, containing list of names, details of email addresses and phone numbers, is given to patients in order to maintain contact with the members of the team they met in clinic.

The diagnosis is given in clinic or through advice letter if the diagnosis is achieved prior or following the clinic appointment. Detailed information is offered to the referring clinician regarding genetic counselling, complications, their treatment and long term management.

On-going follow up is offered to all patients if requested by the referring clinicians or by the patients, if no local service is offered for the patients, in case of extremely rare or novel conditions and in particular for those patients for whom a genetic diagnosis has not been achieved. For these patients, given that informed consent has been obtained, genetic testing of novel genes is performed according to the specific clinical phenotype show by the patient.

**Advisory service**

As a backup to the results obtained, a series of information leaflets have been generated with information about the various forms of LGMD for the patient and clinicians. Information material that was generated in conjunction with the patient charity is regularly reviewed and expanded into new areas.

Advice is available on specific management and follow-up implications (which will be the responsibility of the referring clinician) and the genetic advice appropriate to the patient and other family members. Follow-up analysis of further at-risk relatives may also be indicated. This material is given to patients in clinic and/or to the referring clinician and any other clinicians involved in the care management of the patient.

**Clinical gate keeping for molecular service**

Gate keeping is according to clinical criteria and result of the muscle biopsy analysis. There are some exceptions (i.e. FKRP and LMNA gene), where analysis of the muscle biopsy may not be strictly necessary or even unhelpful, but for these genes we require the relevant clinical history to be provided in order to judge the relevance of the request.

**Public engagement and communication issues**

The service provider is engaging patients, public and patient groups in order to continuously improve the service, its design and what it offers. In this perspective, communication with public and patients group is pivotal. The provider or the service will work with NHS England to ensure sufficient considerations are given to communications. Here are listed some of the recent activities done by NHS England service for LGMDs towards public engagement, communication with patients and patients group:

- Muscular Dystrophy Campaign: The Newcastle Muscle centre has been financially supported by MDC since the mid-1950s. Members of staff contribute to the development of guidelines and information sheets in conjunction with the charity (LGMD factsheets, transition guidelines etc.) and regularly attend information days in conjunction with the patient organisation.
- Survey of NHS patients attending the neuromuscular disease outpatient clinic at the centre for life: Patient satisfaction is routinely monitored for all those patients seen in the NHS clinics.
- The “LGMD-day”: regular days are held on the 28th September 2009, a” Limb Girdle Muscular dystrophy Information Day” was held at the Institute of Human Genetics, International Centre for Life, in Newcastle upon Tyne, hosted by the Newcastle Muscle team.
- Clinical staff are members of the Care group. The team is also working to harmonise efforts for the National Neuromuscular Database with the efforts internationally within Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD).
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**The congenital muscular dystrophies and myopathies**

Two levels of service will be offered.

**Level 1**

The patient **<u>will not</u>** be assessed at the Great Ormond Street Hospital Dubowitz Neuromuscular Centre.

Following detailed clinical information, including comprehensive referral form, letter and /or telephone conversation, muscle and skin biopsy analysis, which includes histology, histochemistry and immunohistochemistry, with electron microscopy and western blot as required will be offered. Alternatively, the stained muscle biopsy slides can be referred for review or second opinion.

A biopsy report is prepared by a consultant pathologist and accompanied by a summary letter from a clinical consultant which summarises the multidisciplinary meeting discussion is sent to the referring clinician, including details of the analysis performed and advice on further management of the patient.

Genetic analysis for the relevant CMD/congenital myopathy genes are performed at Guy & St. Thomas' NHS Foundation Trust, 11 genes responsible for some of CMD and CMY are currently screened. All the genetic reports are collated with the clinical data and forwarded to the lead consultants, who write a summary letter to the referring clinician. Details of muscle biopsy and genetic analysis will be described in Appendix 1.

**Level 2**

Comprehensive assessment for specialised diagnosis and advice to patients and local medical teams. These patients will be assessed at the centre and will undergo:

- full clinical assessment by a paediatric neurologist
- assessment by a specialist neuromuscular physiotherapist
- orthotic, speech therapy and dietetic assessment if indicated
- neurophysiology assessment
- muscle imaging (ultrasound and / or MRI)
- brain imaging (MRI)if indicated
- muscle biopsy
- DNA analysis

**Provision of results and advisory service**

A detailed and personalised plan of intervention for each patient will be generated following the visit to the centre. In addition, a series of parent/patient information leaflets with advice on specific aspects of the condition and of management of the complications will be handed over to the patient and the referring clinicians.
A separate report with the results of the muscle biopsy and genetic testing will be available.
A referral to the appropriate local clinical genetic centre will be recommended.

Patient and parent experience surveys are regularly undertaken by the team, to ensure that the service meets expectations. Through this process we have developed our service to improve information to parents and increase clinical support to the service.

**Congenital myasthenic syndromes**

**Referrals**

Details of the service and route of referral are outlined in the Oxford University Hospitals NHS Trust website. Referrals for outpatient clinics are via GPs or hospital specialists via a downloaded pre-referral form, and are triaged by the clinicians and appointments offered along with a neurophysiology appointment arranged on the same day where necessary. Referrals for DNA sample analysis only go straight to the genetics laboratory and when the initial screen has been performed (i.e. the most likely candidate gene according to the clinical picture) then the clinical team reviews the clinical picture and direct further genetic testing. It may be necessary in some instances to obtain more information or review the patient in clinic. All clinical information will be obtained if possible prior to attendance, from the GP and local physicians/neurologist.

**Outpatient visits**

A detailed outpatient clinical evaluation will be undertaken by the multidisciplinary team led by clinicians assisted by a physiotherapist. The paediatric neurologist will be involved in the treatment of individuals under the age of 16. There are separate paediatric and adult clinics. Clinical investigations that are often required include neurophysiological assessment, rarely muscle biopsy, DNA sample analysis and antibody blood testing for the differential diagnosis of acquired myasthenic syndromes and these are carried out as soon as possible. Where possible (particularly when travelling far) neurophysiological testing and outpatient appointments with other specialists whom we have referred the patient to (e.g. A neurophthalmologist) are arranged for the same day as the OP clinic in order to minimise patient travel and inconvenience.

**Inpatient assessments**

They are not covered by this Service Specification.

**DNA sample analysis**

In some cases the referring clinician requests only DNA sample analysis without outpatient (OP) review by the team. This may be where the patient is unable or unwilling to travel or where the referring clinician is suitably expert in neuromuscular disorders to request appropriate DNA analysis for their specific patient. In such cases DNA testing is performed without seeing the patient and the service asks for clinical information as a means of gate keeping and prioritising requests for analysis. Gene screening is targeted, through an algorithm, dependant upon clinical information from the referral. If the initial target gene is negative the clinical team review data (without funding through this service specification but activity reported) and ask for an update of results or information and prioritise further screening. See section 3.1 for details of the routine genetic screening portfolio.

**Other laboratory assays performed within the research laboratory**

There are a series of non-pathogenic variants as well as pathogenic mutations. The service covers the ability to functionally assess new variants necessary for achieving a definitive diagnosis. This is of critical importance in translation of laboratory findings direct into clinical practice. These include:

- electrophysiology to assess acetylcholine receptor (AChR) channel kinetics for
- fast or slow channel syndromes;
- AChR cell surface expression to test for AChR deficiency syndromes;
- AChR clustering assays to test pathogenicity of RAPSN (gene) and DOK7 (gene) variants;
- exon trapping to test for intronic variants;
- reporter assays to test for promoter mutation;
- expression assays to test CHAT mutations.

Further gene screens of genes encoding the neuromuscular junction proteins MuSK and Agrin and newly identified candidates are available and undertaken where appropriate in the laboratory.

The antibody assay for acetylcholine receptor and MUSK antibodies are available in Oxford as is the new assay for low affinity AChR antibody which is uniquely available in the neuroimmunology research laboratory.

**Remote advice**

In between clinic appointments or regarding patients that are unable to travel the service will offer clinical advice to referring clinicians or GPs on diagnosis, ongoing care and in particular titration of medication doses. This is done by letter, telephone or email, depending upon urgency. The service also offers advice direct to patients, where appropriate, who can phone the service. The myasthenia centre nurse often takes these calls.

The provider will work with NHS England to ensure sufficient considerations are given to communications. Service design is a dynamic process with patients' views on the service, mainly through the patient survey but also informally, instructing this process.

**Muscle channelopathies**

The neuromuscular service is accessible to all families entitled to NHS care at the National Hospital for Neurology and Neurosurgery, which is part of University College London Hospitals NHS trust. Colleagues offer a comprehensive diagnostic and advisory service to patients with a group of neuromuscular disorders known as the skeletal muscle channelopathies. These disorders include conditions such as periodic paralyses [in which patients have episodes of total or partial muscle paralysis] and inherited myotonias [in which patients experience persistent, often disabling muscle stiffness]. All these conditions are treatable but achieving an accurate diagnosis is complex. A precise diagnosis depends on a coordinated

approach which begins with a detailed clinical assessment and often also involves specialised neurophysiological assessment and DNA analysis. An accurate diagnosis is important since this not only allows precise genetic counselling but will also result in the institution of effective treatment. It is common that many patients with these disorders are miss-diagnosed and therefore clinicians from all over the UK are encouraged to refer patients whenever this diagnostic possibility is considered. Effective treatment will significantly improve quality of life for these patients. Furthermore, patients with periodic paralysis are less likely to develop permanent disabling muscle weakness if early treatment is given.

Key elements of the national muscle channelopathy diagnostic and advisory service:

- clinical assessment
- neurophysiological assessment
- DNA analysis.

**Channel clinical service**

The clinical appointment is offered to patients referred because of a personal of familial history of channelopathy or because of symptoms of episodic weakness or muscle stiffness. Many patients have seen many specialists especially those with episodic weakness and some have been considered to have a psychological diagnosis before an accurate diagnosis is achieved in the service. Patients with alternative diagnosis are forwarded to the competent services or relative service if available. When the appointment is arranged, an information letter is sent to the patient

The NHS channel clinical service is a multidisciplinary clinic and the patient will undergo a comprehensive assessment for specialised diagnosis and advice that is structured as follows:

- full clinical assessment by the consultant expert in rare neuromuscular disorders
- muscle assessment by the physiotherapist expert in rare neuromuscular disorders
- muscle MRI may be undertaken
- detailed same day specialised electrophysiological assessment by consultant neurophysiologist
- advice about available clinical, physiotherapy and orthotic treatment and management
- genetic counselling by a neuromuscular specialist nurse
- advice about social care, independent living, benefits, etc by specialist nurse
- DNA analysis
- treatment is commenced following an electrocardiography (ECG) including with either acetazolamide, dichlorpheanmide, mexiletine
- a summary clinic letter is issued.

The diagnosis is given in clinic or through advice letter if the diagnosis is achieved prior or following the clinic appointment. Detailed information is offered to the referring clinician regarding genetic counselling, complications, their treatment and long term management.

On-going follow up is offered to all patients if requested by the referring clinicians or by the patients, if no local service is offered for the patients, in case of extremely rare or novel conditions and in particular for those patients for whom a genetic diagnosis has not been achieved. Treatment monitoring is shared with local specialists depending on local availability. For these patients, given that informed consent has been obtained, genetic testing of novel genes is performed according to the specific clinical phenotype show by the patient.

**Channel advisory service**

As a backup to the results obtain information leaflets will be generated with information about the channelopathies for the patient and clinicians. Advice will be available on specific management and follow-up implications (which will be the responsibility of the referring clinician) and the genetic advice appropriate to the patient and other family members. Follow-up analysis of further at-risk relatives may also be indicated.

**Public engagement and communication issues for channelopathies**

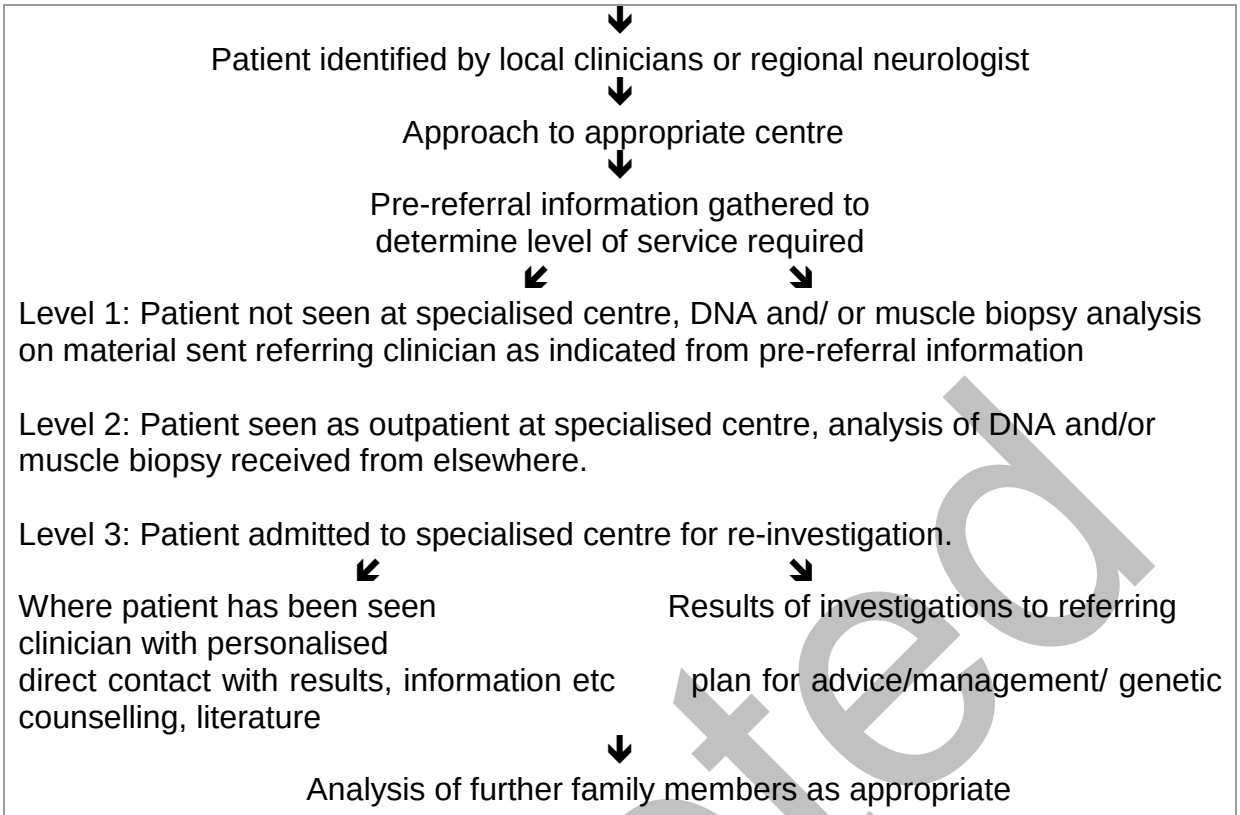
The service provider is engaging patients, public and patient groups in order to continuously improve the service, its design and what it offers. In this perspective, communication with public and patients group is pivotal. The provider or the service will work with NHS England to ensure sufficient considerations are given to communications. Here are listed some of the recent activities carried out by the service for LGMDs towards public engagement, communication with patients and patients group:

- **Muscular Dystrophy Campaign (MDC):** The Queen Square Centre jointly with the Victro Dubowitz Centre is financially supported by MDC
- **Patient survey of the NHS rare neuromuscular Disease outpatient clinic at Queen Square:** Patient satisfaction is routinely monitored for all those patients seen in NHS England funded clinics.
- **Two national channel patient days** have been held at Queen Square Dec 2008 and Dec 2009 attended by over 90 families and very successful. Also attended by NHS England commissioners.
- **British Myology Society** (UK professional body for consultants and senior specialists specialising in neuromuscular diseases) NHS services are regularly presented to the BMS to ensure excellent communications network to all specialist colleagues

**Service model and care pathways**

Because of the subtle differences in the diagnostic approach to these disorders, each is dealt with separately in appendix 2. However, the general approach to the service can be summarised as follows:

National service publicised via doctors and patient organisations




As is clear from the above flow chart, most of the day to day responsibility for the service will be developed in the four service providers (Appendix 2).

**Days/hours of operation**

The laboratory and clinical services operate Mon/Fri 0800 – 1700 hours excluding bank holidays. Inpatient referrals may be received from outside hospitals needing urgent diagnosis and management advice. These are admitted to the relevant care units and hospital wards and cared for primarily by that specialist team, with advice from the neuromuscular consultants.

**Discharge criteria & planning including any transition arrangements**

**Limb-girdle muscular dystrophy**

Patients for which the investigations and the clinical examination exclude a possible diagnosis of LGMD/EDMD/MFM/Etc, and are conversely diagnosed with an alternative genetic or acquired condition are discharged from the service. Undiagnosed patients are not formally discharged and follow up is offered on a case by case basis. In particular, follow up is offered to all patients if requested by the referring clinicians or by the patients, if no local service is offered for the patients, in case of extremely rare or novel conditions and in particular for those patients for whom a genetic diagnosis has not been achieved.

Diagnosed and undiagnosed patients are transferred to local care service with a detailed management plan offered by the NHS England service. Detailed information

is offered to the referring clinician regarding genetic counselling (in case of genetic diagnosis), complications which may accompany the various types of conditions, in particular those affecting the cardiac and respiratory system, physiotherapic management, social services and regional care advisorship.

**CMD and CMY**

Due to the lifelong nature of these disorders, their rarity and the importance of expert surveillance for life-threatening complications such as respiratory failure, feeding problems and major skeletal deformities, multidisciplinary specialist follow up is usually continued on a 6-12 month basis (depending on age and complexity) until age 16-17 years. The NHS England element of this service relates to the initial diagnosis and advice following this diagnosis After the initial follow-up patients are moved into the Clinical Commissioning Group (CCG) service, and can be referred to local providers where appropriate services exist.

Transition to the geographically appropriate adult service is discussed by the age of 16 and between 16 and 17 either a full referral is made to another specialist adult neuromuscular centre, or the young person is seen in a joint adolescent transition clinic with the adult neurology team from the Medical Research Council (MRC) Neuromuscular Centre at the National Hospital for Neurology. A consultant appointment between GOSH and NHNN is in post with particular responsibility for co-ordinating and further developing the transition service.

**Congenital myasthenic syndromes**

Outpatient follow up visits will be arranged at intervals depending on need and may vary from being within months to annually. Patients may be discharged where appropriate to the care of local neurologists or paediatricians where they are stable or where there is no further scope for diagnostic intervention or where there is geographical preference for this. Such transfers shall usually be back to the referring specialist and shall be done by letter. Even after discharge remote advice to local physicians is still available via letter at any point. And patients may re-access the service after many years due to new problems. Many patients require annual follow up with interim care being performed locally.

**Muscle channelopathies**

Outpatient follow up visits will be arranged at intervals depending on need and may vary from being within months to annually. Patients may be discharged where appropriate to the care of local neurologists or paediatricians where they are stable or where there is no further scope for diagnostic intervention or where there is geographical preference for this. Such transfers shall usually be back to the referring specialist and shall be done by letter. Even after discharge remote advice to local physicians is still available via letter at any point. And patients may re-access the service after many years due to new problems. Many patients require annual follow up with interim care being performed locally.

## 2.3 Population covered

The service receives referrals from the UK, Europe and internationally. Those referrals from England and Scotland are funded by the NHSE. Patients from Wales, Northern Ireland and the Channel Islands are subject to separate funding arrangements.

## 2.4 Any acceptance and exclusion criteria

All patients irrespective of sexual orientation, race, religion, disability who are eligible for NHS will be eligible to the service. All usual trust governance procedures as applicable to other NHS patients are applicable to this service too. Pan-trust policies are in place to ensure that the needs of individual patients and their families are met, this includes the patient advice and liaison service (PALS), family accommodation and the use of interpreters. Printed information is available in multiple languages

The provider has 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.

**Referral criteria, sources and routes**

**Limb-girdle muscular dystrophy (LGMD)**

The point of referral into the national service would be the identification of a patient with suspected LGMD or overlapping condition (such as EDMD or MFM), in whom initial investigations had confirmed a muscular dystrophy, but failed through the use of routine local investigations to identify the precise type (dystrophin gene/ protein analysis). The service at Newcastle would comprise examination of the patient where possible, together with analysis of the muscle biopsy using a battery of diagnostic antibodies and both immunocytochemical and immunoblotting techniques. As directed by the protein analysis, subsequent genetic analysis would include mutation detection in the appropriate gene. This could then be extrapolated to the wider family or used to offer prenatal diagnosis if requested.

In a patient presenting with suspected LGMD or overlapping condition, a number of mandatory clinical information are collected in clinics or provided in the pre referral form that accompanies the muscle of DNA sample. The muscle biopsy may be partially informative at the level of histology, suggesting alternative diagnosis. Then with immunohistochemistry or immunoblotting for the specific proteins involved in various forms of LGMD/EDMD/MFMs, the biopsy might suggest a particular disorder. Then, the gold standard for diagnosis is the DNA analysis of the causative gene and mutation.

**The congenital muscular dystrophies and myopathies**

The following specialists are likely to refer their patients to the service: consultant neurologists, paediatric neurologists, paediatricians and Geneticists. It is also possible that some patients will be referred directly via the GP.

Referrals will be made by written letter, with accompanying NHS England referral form. DNA and/or muscle biopsy samples, if appropriate, are sent directly to the relevant lab, as requested on the NHS England referral form.

**Congenital myasthenic syndromes**

There is an on line pre-referral form which requests specific information required to set up the appropriate patient pathway. In addition detailed referral letters are accepted where the appropriate information needed is included; also email information particularly in emergencies are accepted. The pathway is described in section 2.1 under referrals.

**Muscle channelopathies**

The following specialists are likely to refer their patients to the service: consultant neurologists, paediatric neurologists, paediatricians and geneticists. It is also possible that some patients will be referred directly via the GP.

Referrals will be made by written letter, with accompanying NHS England referral form. DNA and/or muscle biopsy samples, if appropriate, are sent directly to the relevant lab, as requested on the NHS England referral form.

**Exclusion criteria**

**Limb-girdle muscular dystrophy**

There are no exclusion criteria for age. Patients with conditions for which a service is offered elsewhere are appropriately referred. Patients with acquired conditions are excluded from the service. The service is not offered to patients with non-rare neuromuscular conditions for which service is offered by the local muscle or genetic service (see section 1.1).

The muscle immunoanalysis unit has a policy of not accepting biopsy samples that have been designated "high risk". These are defined as samples of unfixed tissue from patients who are known to have an infectious or potentially infectious disease that could be fatal if contracted (Hazard Groups 3 and 4). The risk of handling such tissue samples can only be reduced to acceptable levels by a prolonged period (48 hours) of fixation in formalin. This effectively abolishes all immunoreactivity so there are no tests that the unit could undertake on the samples after this treatment

Samples may also be rejected in the following circumstances:

- the minimum essential information is missing from the sample or request form
- the sample and request form information do not match

- the sample is unlabelled or otherwise unsuitable.

**The congenital muscular dystrophies and myopathies**

This service is available for children aged 17 and under who present with symptoms and signs suggesting a congenital muscular dystrophy or myopathy. Geographical coverage for eligibility for NHS England funding is discussed in section 4.1 above

Testing of genes for conditions other than the congenital muscular dystrophies and myopathies are excluded from this specification. (So for example analysis of the rapamycin genes for statin related rhabdomyolysis is excluded.)

**Congenital myasthenic syndromes**

A gatekeeping process is in place which limits inappropriate screening.

**Muscle channelopathies**

This service is available for adults aged 17 and over who present with symptoms and signs suggesting a muscle channelopathy. Geographical coverage for eligibility for NHS England funding is discussed in section 4.1 above

**2.5 Interdependencies with other services**

The purpose of the service is to provide comprehensive, fully integrated, high quality clinical and laboratory services. To achieve this, there is a need for close functional interaction between all the sections within the service, the local trust, with the other NHS centres and the centres around the country and also a need for good communication between genetic services and other relevant clinical specialties, such as cardiologists, ventilation teams, gastroenterologists, orthopaedic surgeons, physiotherapists, ophthalmologists, social care advisors, etc. Interdependencies within each centre are detailed below:

**The limb-girdle muscular dystrophies**

As part of the local neuromuscular team, the LGMD service has a strong integrated role with the local care of neuromuscular patients, with support from the Northern genetic service, the neuropathology team of the Newcastle Upon Tyne Hospitals NHS Trust and the wider NHS Regular meetings are held with professional from the different subgroups of the service (clinical, laboratory) and from other specialties to ensure a high quality and multidisciplinary service. For example, monthly biopsy meetings and diagnostic meetings are held to discuss difficult or complex clinical cases, with support also from the local neuropathology and neurologists from the Newcastle Upon Tyne Hospitals NHS Trust. In particular, patients could be also admitted to muscle biopsy or muscle MRI investigations at the Newcastle Upon Tyne

Hospitals NHS Trust concurrently with the clinical appointment. Joint clinics are also held with other centres, such as for patients with congenital myasthenic syndromes,

as one of the consultants working with the Newcastle muscle team, is a world leading expert in this rare condition. Moreover, the centre has working relationship with the other NHS England services for rare neuromuscular disorders as several conditions go in differential diagnosis with congenital muscular dystrophies (as for patients with mutation in the FKRP gene) or congenital myopathies. In this case, the DNA sample of the patient is forwarded to the appropriate service and if the clinical diagnosis is suggestive for one of these conditions, the patient is referred to the service for a clinical opinion. The NHS England service for LGMDs also receives DNA samples and biopsies for patients with clinical conditions allelic to one of those for which we offer service, such as in case of rare congenital forms of MFM or congenital muscular dystrophies caused by mutations in the LMNA gene.

**The congenital muscular dystrophies and myopathies**

The Dubowitz Neuromuscular Centre incorporates a wide multi-disciplinary team including Paediatric neurology, specialist nursing, physiotherapy, pathology, genetics, family care advisor and therapy services. The team works with other clinical services across Great Ormond Street Hospital for Children NHS Foundation Trust to ensure that complex patients receive a high-level of service, focused around the needs of the child and their family. This includes working in dedicated joint clinics with spinal surgery and orthopaedic colleagues, joint consultations with respiratory, intensive care, cardiology and medical teams from across the hospital and specialist colleagues from other hospitals. Close liaison also takes place with the child's local paediatric servicesJoint adolescent clinics are held with adult neurology colleagues from the National Hospital for Neurology (UCLH) to facilitate transition to the adult service.

Pathology services are provided through the Department of Neuropathology at Institute of Neurology, University College London Hospital in conjunction with the Great Ormond Street Hospital for Children NHS Foundation Trust histopathology department. The Dubowitz Neuromuscular Centre biopsy service acts independently as a paediatric muscle service in the department. There are weekly multidisciplinary clinical and pathology meetings held to review all biopsy referrals to the service. The centre also organises quarterly pan-London muscle pathology multidisciplinary meetings.

The genetic analysis is carried out at the DNA laboratory at Guy's and St Thomas' Hospital NHS Trust (GSTT), and the same NHS England referral form is used between the two sites. DNA samples are sent to Guy's hospital directly but the genetic reports companied by a letter from a consultant are forwarded to the referring clinician from Great Ormond Street Hospital for Children NHS Foundation Trust. Regular joint meetings are held with the Guy's team to discuss service issues such as 'gate-keeping' for genetic studies (to avoid inappropriate referrals) and sharing database information. Regular meetings are also held to discuss service issues, implementation of new genes and other research developments. Flowcharts to allow the clinical scientists on the appropriateness of the proposed genetic testing are available for each of the conditions to be tested and further advice is available by consultants).

**Congenital myasthenic syndromes**

The service is expected to interact with the physicians, GPs, neurologists, patient groups and societies. It is expected to offer remote guidance to local specialists for interim follow up of some patients who live far away (activity not funded but reported).

Onward referral to other specialists is often required for example for respiratory function assessment and should be done either in Oxford or the patients' local hospital depending upon local service availability and/or preference. Should genetic counselling be required , as this is an inherited condition, patients will be referred locally.

**Muscle Channelopathies**

The Queen Square Centre for Neuromuscular Centre incorporates a wide multi-disciplinary team including adult neurology, specialist nursing, physiotherapy, pathology, genetics, and therapy services. The team works with other clinical services across University College London Hospital NHS Foundation Trust to ensure that complex patients receive a high-level of service, focused around their needs. This includes working in dedicated joint clinics with and joint consultations with electrophysiology, cardiology and medical teams from across the hospital and specialist colleagues from other hospitals. Close liaison takes place with patient local services. Joint adolescent clinics are held with paediatric neurology colleagues to facilitate transition to the adult service.

The genetic analysis is carried out at the DNA laboratory at the Queen Square neurogenetics lab. Regular joint meetings are held with the genetics team to discuss service issues such as 'gate-keeping' for genetic studies (to avoid inappropriate referrals) and sharing database information. Regular meetings are also held to discuss service issues, implementation of new genes and other research developments.
The centre works in collaboration with the Muscular Dystrophy Campaign, which provides research funding, advice to families and sponsorship for workshops and for disease specific patient information days, organised by our group.

**Relevant networks and screening programmes**

Close working relationships between the four centres and the NHS centre for Mitochondrial disease (Oxford, London, Newcastle), with regular strategic review meetings and presentations at national and international conferences.

The personnel of the service are actively involved in the British Myology Society and the Muscle Interest Group (MIG) and regularly attend meetings. Members of the service are integrated member of the World muscle society (WMS), whose meetings are held annually, and the European Neuromuscular Centre (ENMC), an international research support organization for neuromuscular disorders, that aims to facilitate communication amongst scientists and clinicians working in the area of neuromuscular disease The main route whereby ENMC facilitates communication and collaboration is via the funding and organization of workshops with regard to a range of neuromuscular diseases including rare LGMDs and many others.

The service has a strong relationship with patients' organization such as the MDC. Moreover, the service also supports and it is supported by the efforts of TREAT-NMD, an international network for people with neuromuscular diseases and professional working in the field.

The Molecular Genetics Laboratory in Newcastle is a full participant in the Clinical Molecular Genetics Society (CMGS) and British Human Genetics Society (BSHG) networks, disseminating best practice to others and evaluating the impact of new technologies on service provision

All centres collaborate closely with the MRC Neuromuscular Centre at NHNN, Queen Square. The Dubowitz Neuromuscular Centre and the MRC Neuromuscular Centre together run an acclaimed yearly 3-5 day combined paediatric and adult neuromuscular course, with attendees from the UK and abroad. In addition, the Dubowitz Neuromuscular Centre organises a three monthly pan-London clinico-pathological meeting with clinicians and pathologists from adult and paediatric neuromuscular services at other London hospitals.

## 3. Applicable Service Standards

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

All laboratory services must be Clinical Pathology Accreditation (CPA) accredited.

**Clinical governance:** the service is involved in clinical governance activity such as:

- clinical audit activity
- patient user and carer experience and involvement
- education training and development – examples of good practice
- research and clinical effectiveness (clinical guidelines, evidence based practice, new developments, training in research and critical appraisal skills, major research undertakings and innovative work with other agencies and organisations, promotion of knowledge and raising awareness of new innovations, examples of good practice)
- risk management and safety.

The application of the principles of clinical governance to this service combines the guidelines produced by NHS England with NHS clinical governance. As such, it aims to establish the essential components of clinical governance across the integrated national service within the framework of local guidelines. As the services involved are so specialised, we are actively involved in developing the gold standards for their application, and as such are equally or more likely to be looking outward to our international collaborators for parallels as within the NHS.

**Clinical audit**

Services have developed a database which facilitates audit of our service. In

addition to the audit of the day to day running of our service, we will attempt to measure and improve practise based on feedback from patients and referring clinicians. As patients will not always have direct contact with the service (more often that will be via the referring clinician) direct indices of patient satisfaction will be difficult to generate. For patients who are seen at the specialised centres, their opinions on the service they receive will be specifically sought. For families dealt with via local clinicians, satisfaction of the referring doctor will be sought. Valid outcome measures will be identified in line with the development of outcome measures generally in clinical genetic practise.

**Competence and training**

Existing clinical governance standards and guidelines within the trust applies at each level. All members of the group are already registered for Continuing Professional Development (CPD) and appraisal within the relevant professional group and will adhere to their requirements. All centres are already actively involved in education and training of other professionals from various speciality groups and enhancing this specifically via information leaflets orientated towards both professionals and patients and their families will be a major aim of the national service.

In addition to the trust mandatory trainings that all members of the service for rare neuromuscular diseases have completed, internal seminars and trainings are also organized. Staff are actively involved in the dissemination of information about neuromuscular diseases to patient-led special interest groups, national and international charities and participating in international meetings.

**Quality standards**

The novel nature of the service provided means that there are no immediately referable quality standards that we can apply without modification. However, there are elements of quality control which are a natural part of the accreditation and quality assurance schemes already in place, so that although the conditions and the specific tests dealt with may be novel, many of the techniques applied can be compared to nationally agreed quality standards, for example via the Clinical Molecular Genetics Society. Within the service as a whole, the development of internal monitoring of quality and reproducibility of results is sought.

**Risk management and safety**

We continually monitor patient safety, in particular through the monitoring of risk incidents. Summaries of all reported incidents are compiled and reports used to identify relevant learning points from incidents in other areas. Key learning is disseminated to relevant staff members in their units as appropriate and progress against actions plans are regularly monitored.

**Response time & detail and prioritisation**

**Limb-girdle muscular dystrophy**

The patient gets an information letter and appointment which will be within 11 weeks

of receiving the clinic letter, Patients may be moved up the waiting list if there is a good reason such as the need for urgent counseling in view of severe clinical conditions, forthcoming medical interventions, pregnancy in progress, or other familial risk.

Muscle biopsy reporting time is within 6-8 weeks. Patient samples may be moved up the waiting list if there is a good reason such as the need for urgent genetic counselling, or because the patient is due to be seen in clinic soon. This should allow the report to be issued in under three weeks. Note: All patients biopsied locally will be treated as urgent.

The reporting time for molecular genetic results is within eight weeks for routine samples and within two weeks for samples designated as urgent.

**Congenital muscular dystrophies and myopathies**

The trust guidance is that all patients must be seen within 18 weeks of referral. However children are seen according to clinical need, The most urgent referrals are seen as day cases or inpatients within 1-2 weeks.

**Congenital myasthenic syndromes**

New outpatient clinics are offered within six weeks as an ideal, urgent cases are seen in the next clinic or as day cases. However many patients choose to wait longer for convenience purposes (i.e. school holidays etc).

DNA sample analysis: aims to be six weeks per gene screen, ten working days for familial mutation test and three working days for prenatal testing for a familial mutation.

**Muscle channelopathies**

New outpatients clinics are offered within six weeks, urgent cases are seen in the next clinic or as day cases. However may patients choose to wait longer for convenience purposes (i.e. school holidays etc).
DNA sample analysis: aims to be eight weeks per gene screen.

## 4. Key Service Outcomes

The service aims to provide accurate diagnosis, including the exclusion of conditions, for patients with suspected forms of rare inherited neuromuscular diseases specified above. The service aims to improve the diagnosis of these diseases and develop protocols for treatment and management of these complex patients.

Specific aims

**The limb-girdle muscular dystrophies**

To provide:

- accurate clinical and laboratory based diagnosis
- genetic counselling
- support to individuals and families, e.g. in decision making about future pregnancies; pre- and post-predictive testing
- 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 chose to specialise in genetics
- education and training for other health professionals including those providing genetic counselling within other specialist services, and for undergraduate and post graduate students
- participation in research and clinical audit
- maintenance of confidentiality of patient and family records.

**The congenital muscular dystrophies and myopathies**

Specific objectives for the service are:

- ensure accuracy of diagnosis
- improve the speed of diagnosis for patients with CMD and CMY
- provide advice to local teams across the NHS to improve diagnosis of CMD and CMY
- provide advice to local teams on the ongoing management of patients with CMD and CMY.

**Congenital myasthenic syndromes**

The purposes and goals of the service:

- make a definitive diagnosis (including prenatal diagnosis where requested)
- treat effectively
- provide information for patients, families and their schools and other health

care professions about CMS
- support the MGA and other charities in providing a support service.

Outcomes:
Activity Levels Reported
- number of new, and follow-up outpatient visits and day case admissions
- number of remote consultations (email, phone)
- number of “DNA reviews” (steering specific genetic tests performed dependent on clinic information)
- DNA activity – number of patients, number of exons analysed
- inpatient activity is also reported although is outside of NHSE funding.

Performance Indicators
- turnaround time for DNA reporting
- patient satisfaction (through questionnaire)
- percentage and number of patients with definite diagnosis.

The service will also audit the
- waiting times for clinics
- waiting times for admission
- geographical data (by Clinical Commissioning Group) - of patients for both clinical and laboratory activities.

**Muscle channelopathies**

**Key elements of the national muscle channelopathy diagnostic and advisory service**

- Clinical assessment
- Neurophysiological assessment
- DNA analysis.

**Patients may attend National Hospital for Nervous Diseases at Queen Square for comprehensive service-level-1 or may have DNA sent only for genetic analysis-level-2**

**Key Aims of the service**

- accurate clinical and laboratory based diagnosis
- commence treatment where indicated
- genetic counselling
- support to individuals and families
- e.g. in decision making about future pregnancies; pre- and post predictive testing
- 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 chose to specialise in genetics
- education and training for other health professionals including those providing genetic counselling within other specialist services, and for undergraduate and post graduate students
- participation in research and clinical audit
- maintenance of confidentiality of patient and family records
- prevent permanent muscle weakness and disability by effective treatment and treatment monitoring.

**Beneficial outcomes for patients**

- accurate diagnosis achieved avoiding further unneeded investigations and NHS cost
- screening for cardiac complications
- genetic counselling and advice and referral for prenatal diagnosis
- advice regarding anaesthetic complications and avoidance
- effective treatment initiated and monitoring advice provided
- prevention of permanent muscle weakness
- exclusion of diagnosis
- support to individuals and families
- accessible information for families, other health professionals and patient support groups
- expert advice to other health professionals and commissioners
- training for clinicians and scientists who chose to specialise in genetics
- education and training for other health professionals including those providing genetic
- counselling within other specialist services, and for undergraduate and post graduate students
- participation in research and clinical audit
- maintenance of confidentiality of patient and family records.

**Outcomes**

Activity levels reported
- number of new, and follow-up outpatient visits and day case admissions
- number of “DNA reviews” (steering specific genetic tests performed dependent on clinic information)
- DNA activity – number of patients, number of exons analysed
- inpatient activity is also reported although is outside of the scope of this service specification.

Performance indicators
- turnaround time for DNA reporting
- patient satisfaction (through questionnaire)

- percentage and number of patients with definite diagnosis.

We will also audit the
- waiting times for clinics
- waiting times for admission.

**5. Location of Provider Premises**

**The limb-girdle muscular dystrophy**

Clinics are held at the Institute for Human Genetics, International Centre for Life, Newcastle upon Tyne.

DNA and Blood samples are processed and analysed by the Diagnostic Molecular Genetics Unit, Institute for Human Genetics, International Centre for Life, Newcastle upon Tyne.

The muscle biopsy service is located at the Muscle Immunoanalysis Unit, Dental Hospital, Newcastle-upon-Tyne.

**The congenital muscular dystrophies and myopathies**

The clinical service is provided at Great Ormond Street Hospital for Children NHS Foundation Trust.

The pathology laboratory is at the Institute of Neurology London, Great Ormond Street Hospital for Children NHS Foundation Trust. The genetics service for analysis of DNA samples is at Guy's & St. Thomas' NHS Foundation Trust, London

**Congenital myasthenic syndromes**

The clinical service and the research laboratory service are located at the John Radcliffe Hospital site, Oxford. Full day joint clinics are held monthly, alternating between Oxford and London (Great Ormond Street Hospital). The genetic service is located at the Churchill hospital site in Oxford.

**Muscle Channelopathies**

The clinical service is at the centre for neuromuscular diseases in Queen Square part of University College London Hospital NHS Foundation Trust. Weekly clinics and same say neurophysiology. Genetics at the Queen Square neurogenetics lab.

**Sub-contractors**

Pathology service at Guy's Hospital (Genetic Analysis)
Institute of Neurology, Department of Neuropathology, UCLH (Pathology service)

**APPENDIX – 1**

**NHSE SERVICE SPECIFICATION**

## Newcastle LGMD Centre - Repertoire of Tests

### Muscle biopsy analysis

Specialized immunoanalysis on sections and/or blots as appropriate to include analysis of the following proteins for direct primary involvement:

- α, β, γ, and δ-sarcoglycans
- Calpain 3
- Dysferlin
- Caveolin 3
- Myotilin
- Telethonin
- Lamin A/C

The following for secondary involvement:

- α-dystroglycan
- Utrophin
- nNOS
- Laminin α5, β1, γ1 chains
- β-dystroglycan
- Ubiquitin
- MHC Class 1

The following for exclusion of alternative diagnoses:

- Dystrophin
- Emerin
- Collagen VI
- Laminin α2, α5, β1, γ1 chains
- Desmin
- Alpha B crystallin
- VCP
- PTRF/Cavin

The following for control:

- β-spectrin
- Myosin heavy chain (neonatal, fast and slow)

Others to be added as developed

- Assessment of stained slides for second opinion
- (This is outwith funding for this contract but activity is reported)
- Slides can be referred either on their own, or prior to referring the muscle biopsy

for further study, or may be requested by our clinicians for review prior to seeing a new patient in the clinic, who has had a muscle biopsy performed at another centre. We request a copy of the pathology report to be sent with the slides, if available.

**The Molecular Genetics Laboratory** provides a fully comprehensive mutation screening service for 18 genes known to be causative of LGMD (*LMNA, FKRP, CAPN3, DYSF, Cav3, SGCA, SGCB, SGCD, SGCG DES, MYOT, CRYAB, FLN-C, FHL1, VCP, GNE, Emerin, ANO5*). In all cases the full gene coding regions are screened using bi-directional fluorescent sequencing. Additional dosage testing is provided using MLPA for *LMNA* and *DYSF*. Where appropriate, bioinformatic tools are used to assist in the interpretation of results.

**Dubowitz Neuromuscular Centre Muscle Biopsy Service - Repertoire of Tests**

The tests that have been carried out are specified in each muscle biopsy report. If slides with good staining quality are supplied, some techniques may not be repeated.

**1. Muscle Biopsy**

**Histology and Histochemistry analysis**

*Routine tests:*

- Haematoxylin & Eosin (H&E)
- Gomori modified Trichrome (TRI)
- Reduced nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR)
- Succinate dehydrogenase (SDH)
- cytochrome oxydase (COX)
- Combined COX/SDH
- PAS Schiff's reagent (PAS)
- Oil Red O (ORO)

**1.2. The following tests will be performed as appropriate to the clinical phenotype and/or after initial analyses**

*Additional tests:*

- Acid phosphatase
- Phosphofructokinase (PFK)
- Myophosphorylase (PPase)
- Myoadenilate deaminase (AMP)
- Menadione-linked $\alpha$-glycerophosphate dehydrogenase (MGD):

**Immunohistochemistry analysis**

*Routine tests:*

- Dystrophin (dys-1, 2 and 3)
- β-spectrin
- Utrophin
- Neuronal nitric oxide synthase (nNOS)
- Neonatal myosin heavy chain
- Fast myosin heavy chain
- Slow myosin heavy chain
- β-dystroglycan
- α-dystroglycan (clone IIH6 )
- Sarcoglycans (α,β,)
- Collagen VI (MAB 1944 and MAB 3303) and double labelling with perlecan if appropriate
- Laminin α2 (80kDa, MAB1922, 300 kDa, Alexis 4H8)
- Laminin α5
- Laminin β1
- Laminin γ1
- Major histocompatibility complex type 1 (MHC-1)

*Additional tests (when appropriate):*
- Laminin β2, (?MDC1A)
- NCAM
- Dysferlin (Hamlet, Hamlet-2)

*Emerin*
- Lamin A, Lamin A/C, Lamin B1 and Lamin B2
- Laminin-α2 (NCL-Mer antibody)
- Myotilin,
- Caveolin3
- Desmin

*Cardiac actin*

*Nebulin*
- Actin
- α-actinins
- Serca1 and secra 2

*The diagnostic value of immmunoblotting is currently being assessed for*
- α-dystroglycan (IIH6)
- β-dystroglycan
- Laminin-α2 (MAB1922)
- RYR1

*Electron microscopy (EM)*
Ultrastructural analysis of muscle by electron microscopy is an important technique in the differential diagnosis of congenital myopathies. In addition to preparation of in-house muscle biopsy samples for EM, we accept the resin blocks, grids or EM photographs of biopsies performed at other centres for review.

- Assessment of stained slides for second opinion
- Slides can be referred either on their own, or prior to referring the muscle biopsy for further study, or may be requested by our clinicians for review prior to seeing a new patient in the clinic, who has had a muscle biopsy performed at another centre. We request a copy of the pathology report to be sent with the slides, if available.

**2. Skin Biopsy**

Where muscle biopsy is not available, immunohistochemistry of a frozen skin biopsy sample may help confirm some clinical diagnoses, notably MDC1A.

- Laminin-α2 (80kDa MAB1922, 300 kDa Alexis 4H8)
- Laminin -α5
- Laminin -β1
- Laminin -γ1
- Laminin ß2

**Additional:**

- Laminin -α2 (NCL-Mer antibody)
- Emerin

**3. Skin Fibroblast**

When muscle biopsy is not available, immunohistochemistry of cultured fibroblasts may support a clinical diagnosis of Ullrich CMD (UCMD)
Collagen VI, (antibodies: clone MAB 1944 and MAB 3303 )

**4. Chorionic Villus Sample (C.V.S.)**

Prenatal diagnosis is carried out using immunohistochemistry for some CMD subtypes, in combination with linkage or DNA analysis

- Collagen VI (MAB1944, MAB 3303)
- Laminin-α2 (80kDa MAB1922, 300 kDa Alexis 4H8)
- Laminin -α5
- Laminin -β1
- Laminin -β2
- Laminin -γ1

**5. Genetic Analysis**

Genes currently offered for CMD/CMY funded by NHS England:

- LAMA2
- SEPN1
- POMT1
- POMT2

- FKRP
- POMGnT1
- LARGE
- Fukutin
- COL6A1 & COL6A2 & COL6A3
- RYR1
- ACTA1

**Haplotype analysis (at the corresponding loci for the following forms of Congenital muscular dystrophy):**

UCMD (only for families with known recessive inheritance, since dominant and *de novo* COL6 mutations are common) and MDC1A

**Channelopathy Service - Repertoire of Tests**

(Highlighted in yellow)

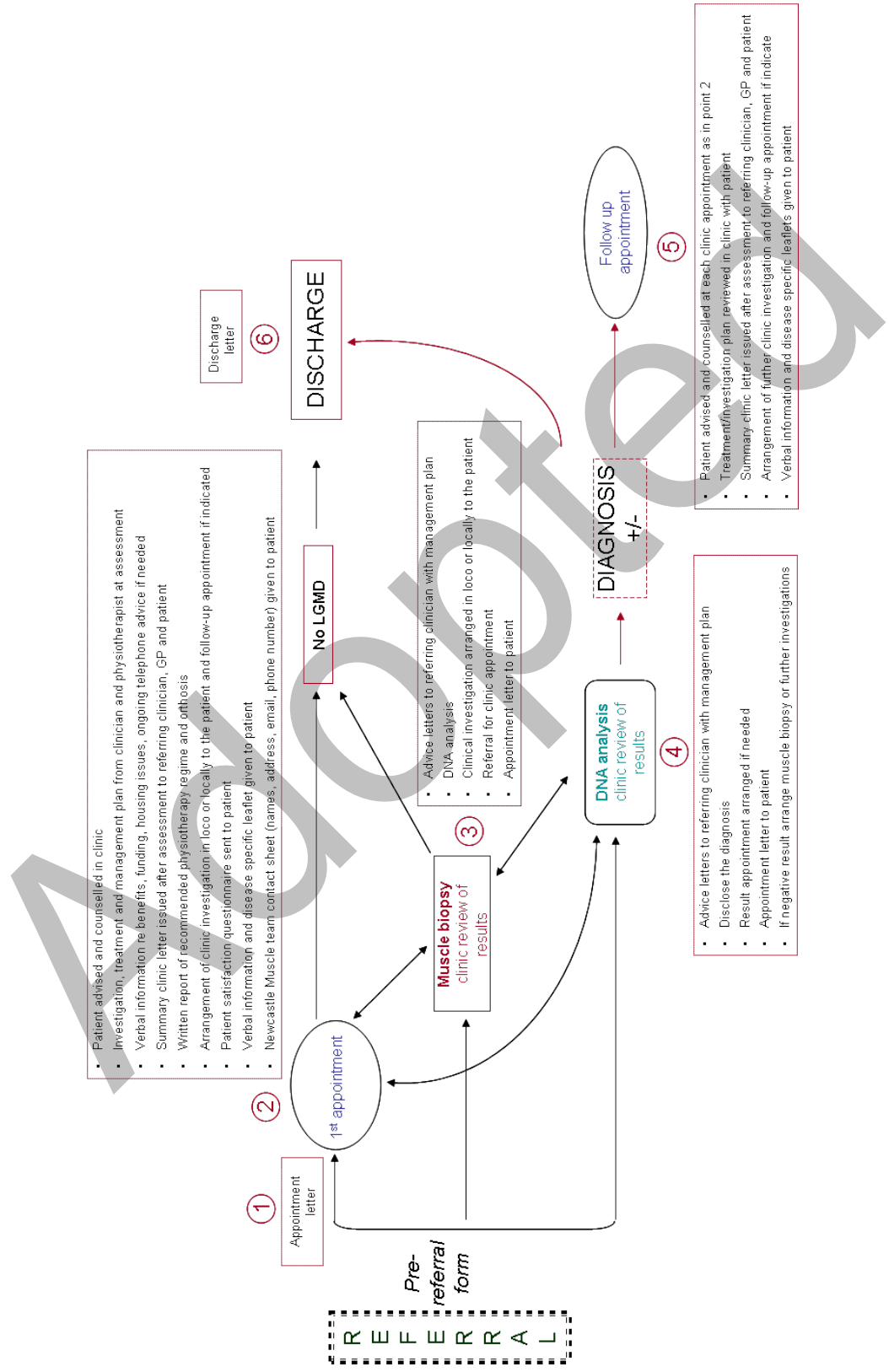
t Table 1 The human voltage-gated ion channelopathies

| Ion channel | Examples of disorders | Gene | Chrom |
|---|---|---|---|
| Na+ channel a subunit | Hyper and hypokalemic periodic paralysis paramyotonia congenita and sodium channel myotonia | SCN4A | 17q |
| | Long QT syndrome type 3 | SCN5A | 3p |
| | Generalised epilepsy with febrile seizures plus type 2 | SCN1A | 2q |
| | Benign familial neonatal convulsions | SCN2A | 2q |
| | Severe myoclonic epilepsy of infancy | SCN1A | 2q |
| | Inherited erythermalgia | SCN9A | 2q |
| Na+ channel b subunit | Generalised epilepsy with febrile seizures plus type 1 | SCN1B | 19q |
| Ca2+ channel (L-type) | Hypokalemic periodic paralysis malignant hyperthermia | CACNA1S | 1q |
| | Congenital stationary night blindness type 2 | CACNA1F | Xp |
| Ryanodine Ca2+ channel | Malignant hyperthermia central core disease | RYR1 | 19q |
| Ca2+ channel (P/Q-type) | Episodic ataxia type 2 familial hemiplegic migraine Spinocerebellar ataxia type 6 | CACNA1A | 19p |

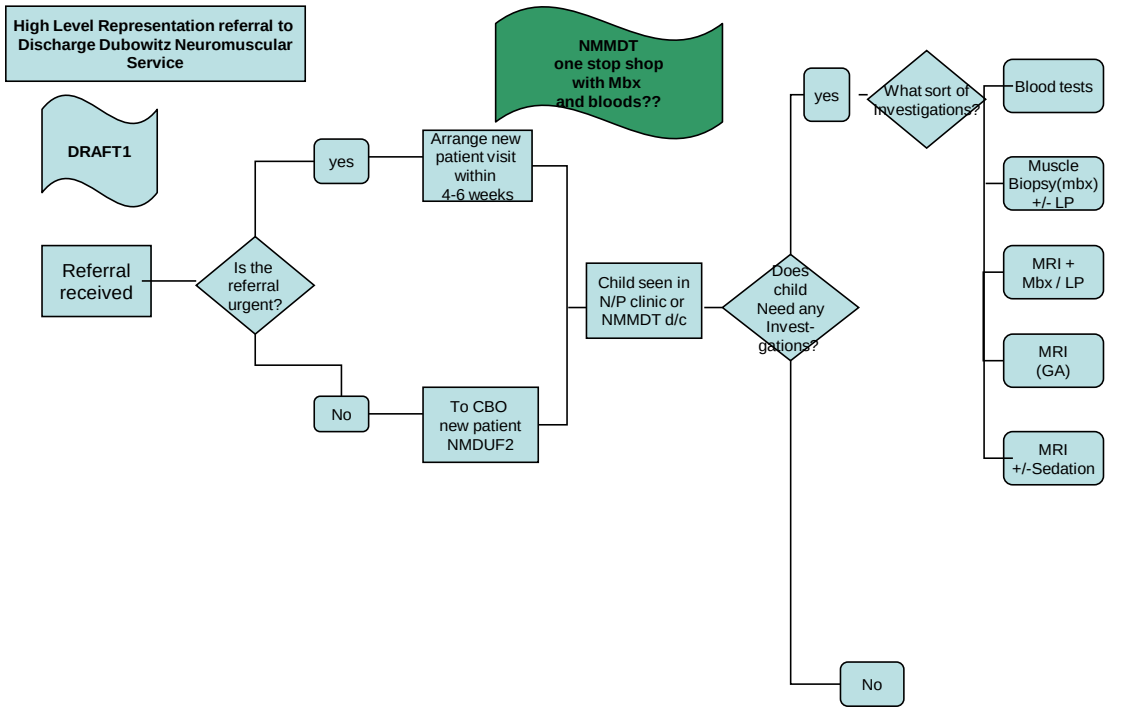
| | |
|---|---|
| Ca2+ channel b subunit Episodic ataxia type 2 CACNB4 juvenile myoclonic epilepsy | 2q |
| Cl2 channel Myotonia congenita CLCN1 (dominant and recessive) | 7q |
| Childhood absence epilepsy CLCN2 | 3q |
| Dent disease CLCN5 | Xp |
| Bartter syndrome type III CLCNKB | 1p |
| K+ channel a subunit Episodic ataxia type 1 KCNA1 | 12p |
| Long QT syndrome type 2 HERG | |
| Andersen–Tawil syndrome KCNJ2 (long QT type 7) | 7q |
| Susceptibility to thyrotoxic periodic paralysis KCNJ18 | 17p |

## APPENDIX – 2

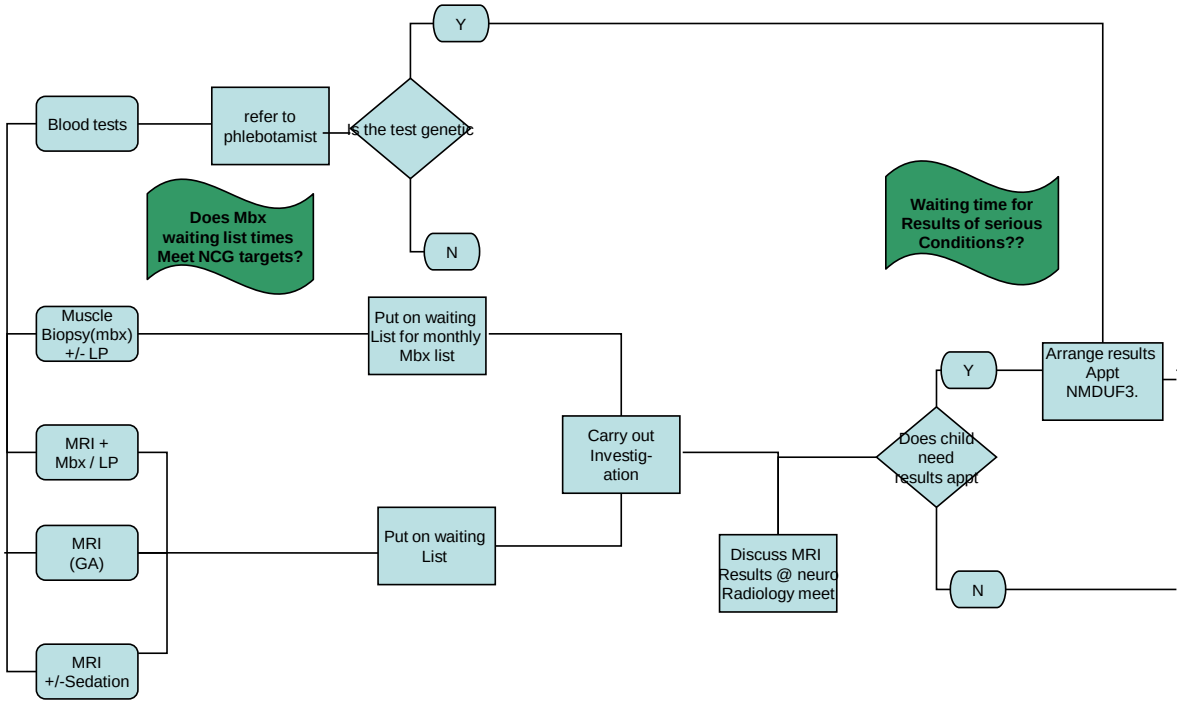
## NEWCASTLE LIMB GIRDLE MUSCULAR DYSTROPHY – PATIENT CARE PATHWAY



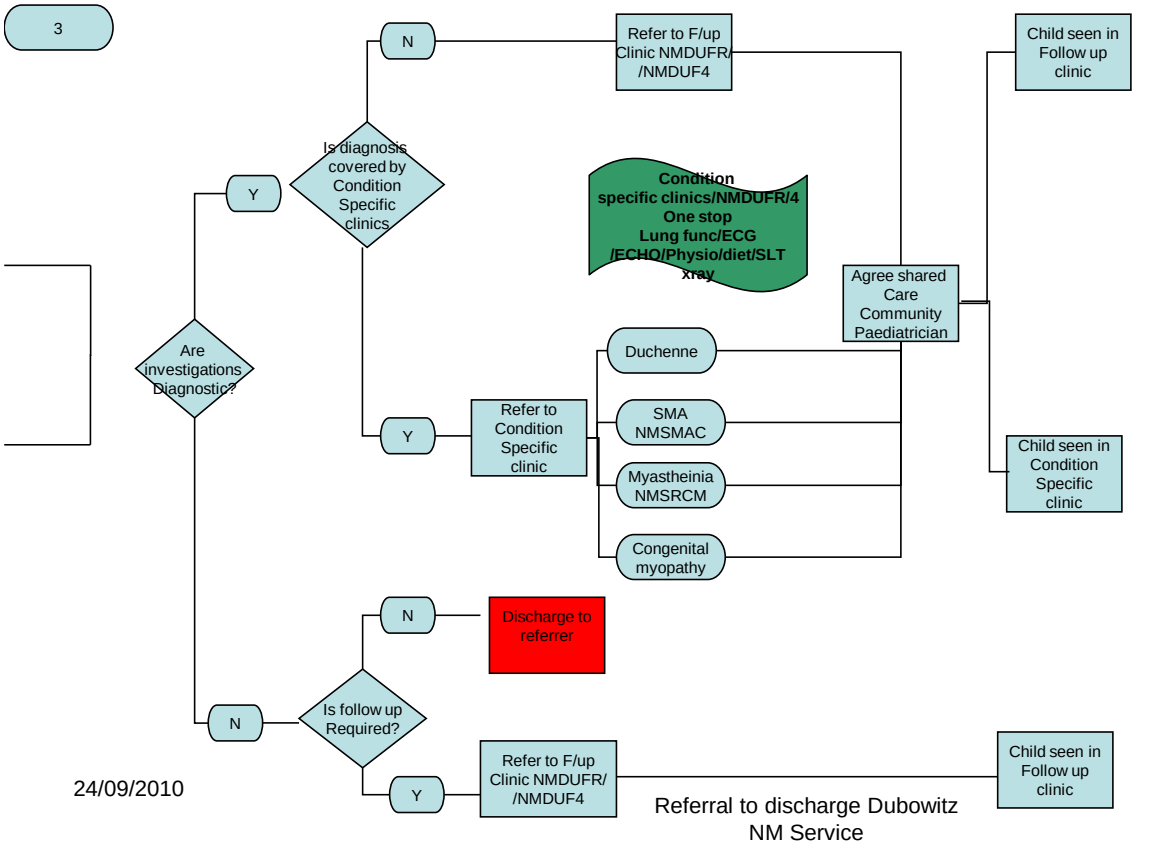
## DUBOWITZ NEUROMUSCULAR CENTRE FOR CONGENITAL DYSTROPHIES AND MYOPATHIES - PATIENT CARE PATHWAY

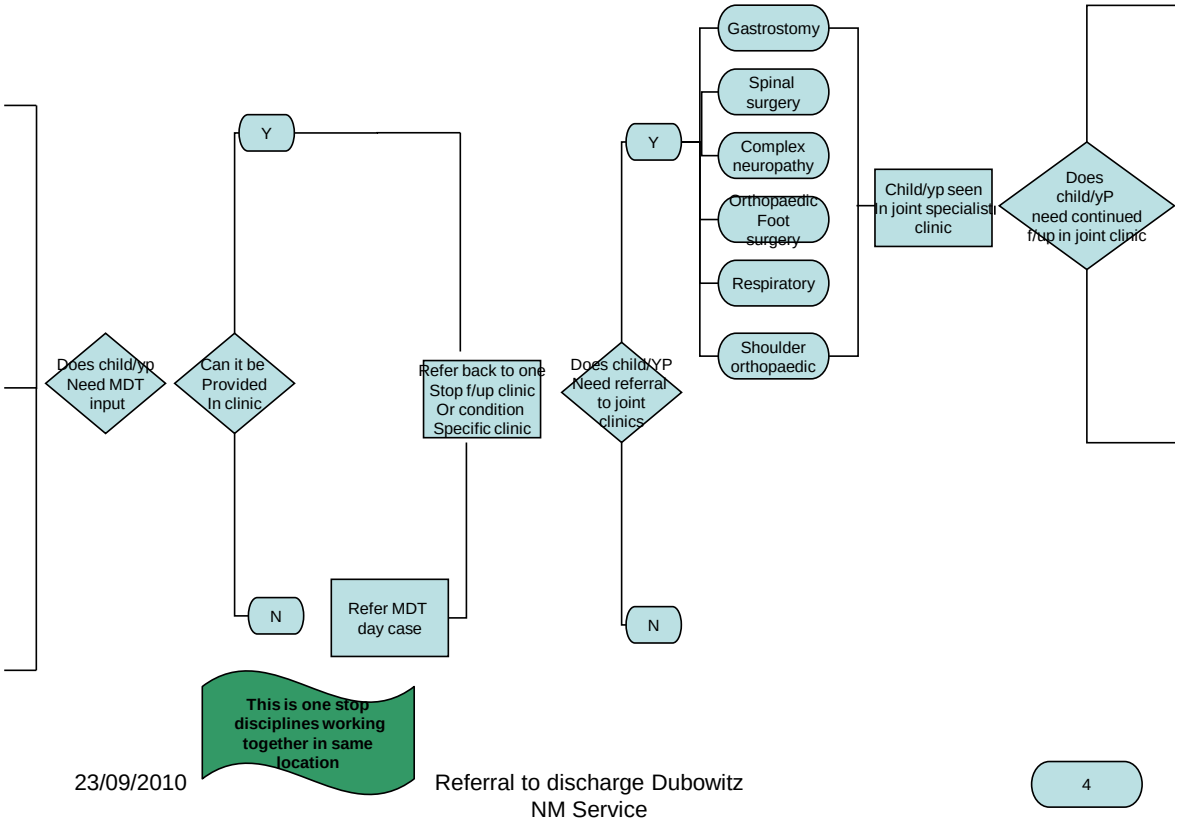



23/09/2010 Referral to discharge Dubowitz NM Service 1

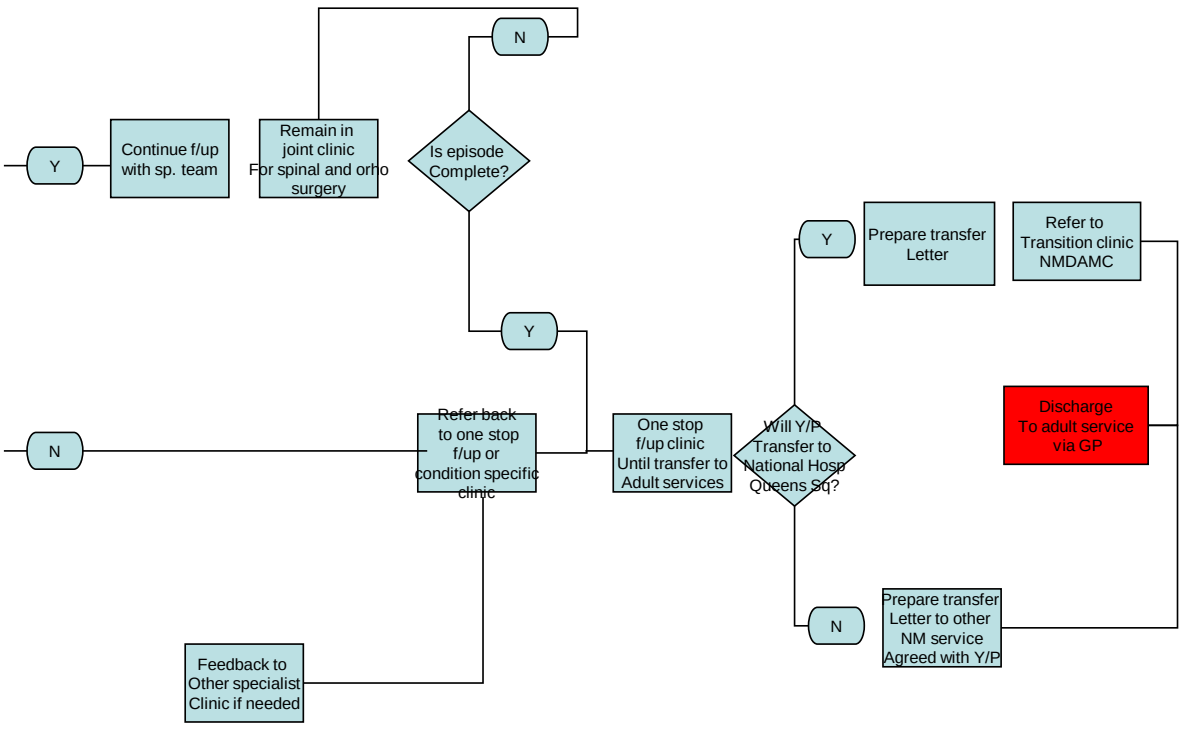




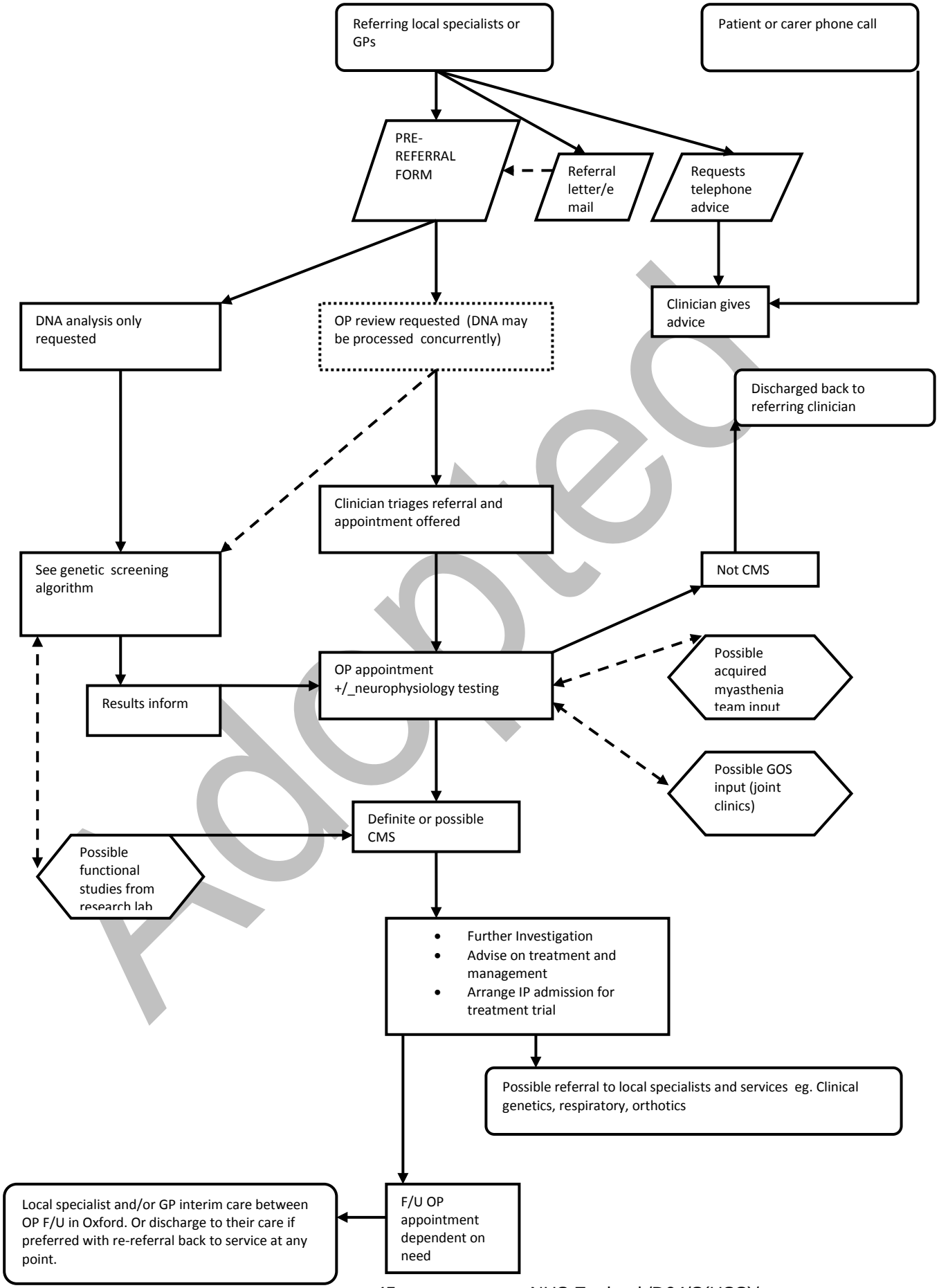



23/09/2010 Referral to discharge Dubowitz NM Service 4




24/09/2010 Referral to discharge Dubowitz NM Service 5

## OXFORD CONGENITAL MYASTHENIC SYNDROMES – PATIENT CARE PATHWAY



## QUEEN SQUARE CHANNELOPATHIES – PATIENT CARE PATHWAY

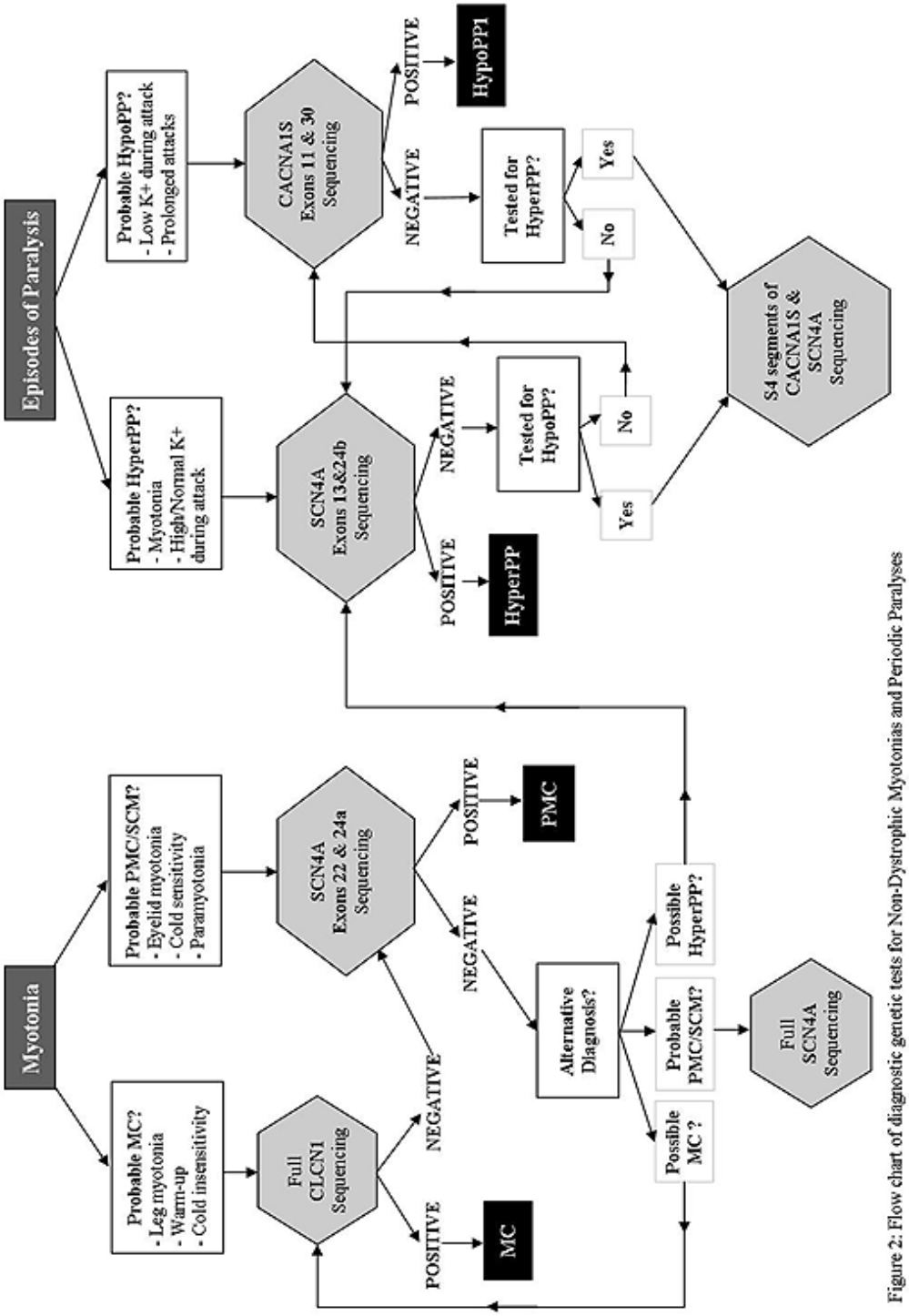



Figure 2: Flow chart of diagnostic genetic tests for Non-Dystrophic Myotonias and Periodic Paralyses

QUEEN SQUARE NHSE INERGRATED ELECTROPHYSIOLOGY GENETIC TESTING PROTOCOL FOR MUSCLE CHANNELOPATHIES

Suggested algorithm when using electrophysiological exercise tests for guiding genetic testing in patients with suspected nondystrophic myotonia DM1 5 myotonic dystrophy type 1; DM2 5 proximal myotonic myopathy; MC 5 myotonia congenita; PMC 5 paramyotonia congenita; SCM 5 sodium channel myotonia.