

# **GENETIC SERVICES FOR NEUROLOGICAL DISORDERS**

Report of a working group of Association of British Neurologists and Clinical  
Genetics Society

## **SUMMARY**

Neurological disorders, both of adult life and childhood, include a considerable proportion that are genetically determined, many of which follow single gene Mendelian inheritance and can give high risks for family members. Many of the underlying genes have been isolated, making genetic testing feasible.

Although research into neurogenetics in the UK has been strong, genetic services for neurological disorders have developed in an uncoordinated way. A wide range of diagnostic and management clinics has been established, but with no specific funding provision within either genetics or neurological services in most centres.

Neurogenetics forms an important part of clinical practice in both adult and paediatric neurology, as well as in clinical genetics, particularly in specialist centres. Likewise, laboratory molecular genetics services provide an increasing range of analyses for both primary diagnosis and prediction.

The working group, composed of neurologists (adult and paediatric), clinical geneticists and genetic counsellors, members of lay societies, and representatives from laboratory medicine and public health, has made the following recommendations. Their numbering refers to the specific chapter in the full report.

The report was approved by the Councils of the two Societies in September 2003.

## Recommendations

- 3.1 Specialist neurogenetics diagnostic clinics, usually run jointly by a clinical geneticist and neurologist (adult or paediatric), form a valuable activity that supports and enhances both neurology and clinical genetics services. The majority of teaching centres have such a clinic; we recommend that existing clinics are strengthened, supported and formally designated and that they are established where they do not yet exist.
- 3.2 We recommend that each centre has a designated consultant clinical geneticist and neurologist (involving where possible those with paediatric as well as adult expertise in the field) to take overall responsibility for the running and development of neurogenetics clinics and other clinical services in the field with nurse specialist or genetic counsellor input to ensure ongoing patient support.
- 3.3 Detailed recommendations on laboratory genetics services for inherited neurological disorders are not within the remit of this working group, but we emphasise the importance of these services, their development in a co-ordinated, equitable and effective manner, and that staff involved with clinical aspects of neurogenetics should be closely involved in this process.
- 3.4 We strongly support current laboratory developments, such as the UK genetic testing network for rare disorders, that should help to extend the range and ensure the quality of genetic testing for inherited neurological disorders and to promote the transfer of testing from research into service. We suggest that for some of the rarer disorders we should also look outside the UK and work with our European partners for the effective and equitable development of services on a Europe wide basis.
- 4.1 Most genetic counselling referrals which include a neurological component do not require a specialist neurogenetics service, but are appropriately handled by general medical genetics services or in straightforward situations, by general neurologists and family doctors.

- 4.2 A specialist neurogenetics clinic, involving both clinical genetics and neurology staff, is of considerable value in establishing a precise diagnosis in situations of diagnostic uncertainty or rarity, thus allowing an accurate foundation on which genetic counselling can be based. They can also advise on the use of complex pathways of diagnosis which may require the integration of molecular genetic and other testing modalities.
- 5.1 Presymptomatic testing for late onset neurogenetic disorders (eg for Huntington's disease) is a particularly complex activity, requiring medical and genetic counselling staff with particular experience in this area; it should be recognised as part of specialist neurogenetics activity.
- 6.1 Prenatal diagnosis of childhood neurological disorders requires close liaison between paediatric neurologist, clinical geneticist and the specialised laboratories (both genetic and biochemical), needing to be involved in this complex group of rare disorders.
- 6.2 Prenatal diagnosis for serious adult neurogenetic disorders is an uncommon but important option for families. It is best handled in conjunction with discussions of presymptomatic testing and by the same specialist staff, linking with fetal medicine services.
- 6.3 Pre-implantation diagnosis remains a very limited service requiring both a high degree of expertise in testing for the particular disorder and close links with clinical genetics services. Neurogenetic disorders do not currently need specific arrangements, but specialist neurogenetic services need to be fully informed of current and emerging possibilities in this field so that their patients have access to these services if required.
- 7.1 Management of many neurogenetic disorders is frequently complex, with aspects specific to individual disorders or disease groups, giving considerable benefit from specific management clinics led by staff with specialised neurogenetics expertise.

- 7.2 Specialised neurogenetics management clinics require clearly designated organisation, staffing, funding and support. Multidisciplinary involvement is frequently needed.
- 7.3 These clinics should form part of the recognised remit of Neurogenetics and involve co-operation between Neurology and Genetics services.
- 7.4 Clinics may appropriately serve patients from a wide geographical area and may need to do this to give critical mass of experience. Geographical equity across the UK is an important consideration in planning these specialised clinics and strengthening and properly supporting those that already exist.
- 8.1 Management of many neurogenetic disorders is frequently complex, with aspects specific to individual disorders or disease groups, giving considerable benefit to specific management clinics led by staff with specialised neurogenetics expertise.
- 8.2 Specialised neurogenetics management clinics require clearly designated organisation, staffing, funding and support. Multidisciplinary involvement such as physiotherapy and occupational therapy is frequently needed.
- 8.3 In most instances, such clinics will form part of a designated neurogenetics service.
- 8.4 Clinics may appropriately serve patients from a wide geographical area and may need to do this to give critical mass of experience. Geographical equity across the UK is an important consideration in planning these specialised clinics.
- 9.1 Specialist neurogenetics services currently have only a minimal role in relation to common neurological disorders, a situation unlikely to change in the near future.

- 9.2 A small but important specific area requiring awareness, recognition and specialist referral is that of the uncommon single gene subset of families occurring within a much larger grouping of a common disorder.
- 9.3 Clear and accurate information on genetic risks needs to be available for general neurologists and family doctors, to allow them to respond to patient enquiries and avoid inappropriate referrals.
- 9.4 Molecular genetic tests have no validated service role at present in testing for susceptibility to common neurological disorders, unless a rare mendelian subtype is suspected.
- 10.1 Family doctors need to be familiar with the broad principles of genetics in relation to inherited neurological disorders, rather than the details of individual rare conditions. They also need to be familiar with and use appropriately the specialist services in their area.
- 10.2 General neurologists, in particular paediatric neurologists, need a significant exposure during their training to the genetic issues posed by inherited neurological disorders, while trainees in clinical genetics will benefit from familiarity with the clinical aspects of these disorders. Specific shared training days at supraregional level should help with this.
- 10.3 Specific and detailed training programmes need to be established for those geneticists and for adult and paediatric neurologists aiming at a career in neurogenetics. Such programmes should be shared between the parent specialties; there already exists a wide range of activities for them to be based on, but this requires extending and defining more clearly.
- 10.4 An annual national neurogenetics training meeting is suggested as a specific event for trainees across the UK, including genetic counsellors specialising in this field.

- 10.5 There are currently no NHS training posts specifically or even partly designated in relation to neurogenetics. These need to be created (either within the existing complement or as additional posts) in each teaching centre providing specialist genetic services for neurological disorders. Initially they should be based in centres with particular expertise and rotation could be arranged to maximise experience. They should be open to trainees in either clinical genetics or neurology (adult or paediatric).
- 10.6 Consultant posts with neurogenetics as a defined subspecialty, in both clinical genetics and neurology (adult or paediatric), will be essential if doctors are to take up training posts in the field.
- 11.1 Research and other academic activity in relation to genetic aspects of neurological disease is of high quality in the UK, but is hindered by the lack of clearly defined and supported NHS clinics and other facilities for neurogenetics services.
- 11.2 Current research training posts in neurogenetics should include elements of service-related training posts. Research and NHS training posts should be constructed to allow movement between each type of post so as to give flexibility in pursuing an NHS based or academic consultant career.
- 11.3 Specialist neurogenetics clinics (both diagnostic and management) offer considerable potential for the understanding and better therapy of uncommon neurogenetic disorders and should be planned and staffed to facilitate these developments.
- 11.4 Creation of specific clinical academic posts in neurogenetics, preferably joint or closely linked between the parent specialties, will have an important role in promoting development of the field and encouraging able people to enter training in it, as will academic recognition of senior NHS staff already in the field.

- 12.1 At primary care level, no major organisational, staffing or commissioning changes are needed, since until service implications arise in relation to common neurological disorders, impact at this level will be slight. There will be a small cost for the educational aspects and practice guidelines recommended.
- 12.2 No significant changes in organisation are recommended at secondary level, in relation to general adult and paediatric neurologists and clinical geneticists. Training implications will have a specific cost that will need to be shared between clinical genetics and Neurology training budgets and which will have time implications for senior specialist staff.
- 12.3 The principal recommendations of this report are at tertiary level and rest on the recognition of a specific subspecialty (but not full specialty) of clinical neurogenetics within the NHS. That subspecialty should have the remit to provide specialist genetic services for neurological disorders, together with a co-ordinating and educational role in this field extending to secondary and primary care. The commissioning implications are that within the genetics, neurological or paediatric specialised services definitions, activity in neurogenetics should be explicitly recognised as coming within those definitions.
- 12.4 Any recognised subspecialty of clinical neurogenetics should be open to appropriately trained and experienced clinicians whose primary specialty is either clinical genetics, adult or paediatric neurology.
- 12.5 The satisfactory development of this subspecialty will require the active co-operation of the parent specialties, probably through a specific committee and involving the appropriate specialist societies.
- 12.6 The specialist activities of consultants currently working in the field should be specifically designated and recognised within existing commissioning mechanisms, so as to avoid these services being lost with retirement or movement of senior staff.

- 12.7 Where existing services are absent or deficient, creation of new consultant posts, or allocation within an existing complement, should be undertaken to fill these deficiencies.
- 12.8 As a minimum, for a population of 2 million, we recommend that there is one designated post (or full time equivalent) based within clinical genetics and one based in neurology (either adult, paediatric or in combination) to provide consultant leadership. It may be appropriate for this staffing to be shared between consultants with different specific expertise (eg: neuromuscular and CNS disorders, paediatric neurology and adult neurology).
- 12.9 The role of specialist neurogenetics consultants should include not only the running and development of specialist neurogenetics clinics (diagnostic and management) and the development of guidelines for non specialist staff at secondary and primary care levels, but a more general educational and coordinating role in the development of the field, as well as involvement in audit and in research.
- 12.10 Specialist neurogenetics clinics will require definition of support required in terms of both staff and facilities. In particular, the role of nurse specialists/counsellors will be a valuable resource in those areas not specifically requiring a medical training, including specific aspects of genetic counselling and management.
- 12.11 The majority of the above recommendations can, at least in part, be implemented by the specific recognition and utilisation of existing staff and their activities. It would be unwise to estimate additional costs until this first step has been taken.

## **GENETIC SERVICES FOR NEUROLOGICAL DISORDERS**

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## 1. **BACKGROUND AND INTRODUCTION**

1. This working group was established and approved by the councils of Clinical Genetics Society (CGS) and Association of British Neurologists (ABN) in late 2001, with the following remit:

To examine the provision of genetic services for neurological disorders in terms of current practice, staffing, training and commissioning arrangements.

To determine how services might be improved in response to continuing research developments in the field and changes in the National Health Service.

To make recommendations.

It was also agreed that the emphasis of the working group should be on clinically based services, rather than attempting to make detailed laboratory recommendations.

2. Professor Peter Harper was asked to chair the working group, membership was determined in January 2002 (see appendix) and a meeting of the full group held in March 2002. Membership aimed to reflect the range of the specialties involved: not only clinical genetics and neurology (including paediatric neurology), but patient group representatives, a genetic counsellor and a trainee clinician. A laboratory representative was also included, though the working group was not intended to cover laboratory genetic services in detail. Following this, a number of informal subgroups were defined, who worked together, principally by email on particular areas, leading to a draft document in February 2003. Comments were received and incorporated into a more definitive draft, sent to members and the parent societies in May 2003.

3. The field of neurological disorders includes a considerable number of conditions that are genetically determined: by comparison with other systems a relatively high proportion follow mendelian single gene inheritance, often giving high risk for relatives and clear patterns of inheritance. Many specific genes have now been identified, allowing accurate molecular diagnosis and prediction.

4. Historically, neurogenetic disorders have always been prominent in clinical genetics practice and this has increased with the advent of molecular approaches. Many of the first disorders for which the genetic defect were known were neurological, and a significant proportion of the disorders for which routine genetic testing can be performed also fall into this group. There has been a long and distinguished record of neurogenetic research in the UK, both from Genetics and Neurology, while more recently growing numbers of neurologists have become much more involved in applied genetic aspects, with increasing use of molecular tests in primary neurological diagnosis.

5. Mendelian neurological disorders are not only numerous but very diverse. Main groups include:

1. Neuromuscular disorders of childhood and adult life
2. Adult neurodegenerative disorders
3. Early childhood developmental and metabolic disorders

6. All adult neurologists will have a certain exposure to the diseases in the first two categories, while some adult neurologists have developed specific expertise; they are a frequent source of referrals to clinical geneticists. The third group of disorders comprises a major part of the workload of paediatric neurologists, and of those clinical geneticists having special expertise in neurodevelopmental disorders.

7. Common neurological disorders, in which genetic components may be only a part of a complex multifactorial causation of disease, are less amenable at this stage to genetic testing, as the genetic components frequently are not clear, though in some, significant though rare subsets of these disorders have been identified that are determined by single genes.

8. Over the past 30 years genetic services for neurological disorders have developed in a variable and ad hoc way across the UK (and the rest of the world), often influenced by the presence of single individuals with particular research interests or skills. Unlike, for example, cancer genetics there has been no clear plan or recommendations as to how services might develop and as to how clinical genetics

and Neurology might best co-operate to ensure full and geographically equitable service development, or how best to encourage those in training with interest in the area to develop their skills and use them at consultant level.

9. The principal areas covered by the working group are reflected in the subsequent sections of this report. After assessing the current state of services in the UK, the topic of neurogenetic diagnosis is examined in more detail, followed by the specific areas of genetic counselling, presymptomatic testing and prenatal diagnosis. Management and therapy of inherited neurological disorders is included as being intimately connected with diagnostic aspects through the staff involved and current service structures.

10. A specific section on the patient and family perspective reflects the importance of highlighting this, emphasised also by inclusion in the working group of two patient association representatives, one for a central nervous system disease, the other for a neuromuscular disorder. By contrast, the field of common neurological disorders is covered relatively briefly, as at present there is little application of genetic services to them, a situation that does not seem likely to change in the immediate future, though in the longer term (>10 years) this will probably be different.

11. The subject of training is a crucial one for the future of neurogenetics and a series of practical suggestions are made for different groups. The research and academic area is also of particular importance as it currently underpins much of the work and even the services in the field.

12. Finally, a section is devoted to staffing and funding requirements for satisfactory genetic services for neurological disorders, and to the commissioning arrangements needed to support these.

13. Underpinning the entire report is the important conclusion that the effective development of genetic services for neurological disorders is dependent on the continuing close collaboration between the parent specialties of clinical genetics and neurology (including both adult and paediatric neurology), and that the contribution of both is essential. While the foundations for this already exist in most centres, current

structures are largely informal, inadequately supported and variable across the country, making them vulnerable to changes in staff or NHS structures. Equally, the lack of defined training schemes or of a clear role for neurogenetics at consultant level is deterring able trainees in both neurology and genetics from taking it up.

14. Thus the primary aim of this report is to recommend and promote a clearer, though still flexible structure for genetic services for neurological disorders, utilising the skills and interests of clinical geneticists and neurologists (both adult and paediatric). While this will remain based principally at specialist centres, it must be seen in the context of NHS services as a whole, and must include in its development all those groupings involved with genetic aspects of neurological disease.

## **2. THE CURRENT UK SITUATION FOR UK NEUROGENETICS SERVICES**

1. If satisfactory recommendations are to be made for the future, it is essential that there is an accurate picture of current services in the field. The working group has addressed this by a specific questionnaire on specialist neurogenetic clinics, while an earlier questionnaire under the auspices of ABN examined the availability of the molecular laboratory services for inherited neurological disorders (see Section 3).

The clinical services questionnaire was sent to 31 regional genetics centres and had 19 responses (61%). The main findings are summarised here.

2. Clinic provision included 'generic' neurogenetic clinics and clinics for specific inherited neurological disorders, most frequently for neuromuscular disorders (9 clinics) and HD (9 clinics). Remit of these clinics varied between purely diagnostic and management orientated. Structure also varied greatly, with some (mainly management clinics) being highly multidisciplinary. All but one centre had at least one clinic.

3. Genetic counselling referrals for neurological disorders were found to be principally dealt with through the regional genetics service structure, with many families seen in district based genetics clinics to maximise ease of access (see Section 4).

4. Staffing showed a lack of clearly designated consultant staff with responsibility for Neurogenetics, either from Neurology or Genetics, apart from the centres at Newcastle and Queen Square London, where the responsibility was primarily national rather than regional in its remit. By contrast, all responding centres but one could identify both a neurologist and a geneticist with special interest in the field, while a paediatric neurologist with special interest was identified in 12 centres.

5. In addition to medical staff, nurse specialists and other staff from professions allied to medicine were involved in the running of a number of disease specific

clinics, based in either neurology or genetics. Some of these posts were funded by patient associations (See Section 8).

6. Funding was almost universally non-specific, and not dedicated to neurogenetics. A significant number of consultant level posts were University based, with a primary remit in research. There was no specific regional NHS funding for regional neurogenetics clinics or other activities, these forming part of the more general genetics or neurology budgets.

Training is discussed in Section 10.

7. Laboratory neurogenetics services

Since the original ABN survey two years ago there has been radical change in the provision of molecular genetics services for rare disorders, including neurogenetic disorders. The new UK Genetic Testing Network has identified tests for rare disorders offered in UK laboratories and relevant conditions are summarised in Table 2.1, while Table 2.2 lists the ‘core’ tests provided by most centres.

8. Access to testing for inherited neurological disorders is not formally restricted to particular groups of clinicians. However, at present presymptomatic testing for late onset neurogenetic disorders is undertaken mainly by clinical geneticists, whereas diagnostic use in symptomatic patients is principally requested by neurologists, and to a lesser extent by other clinical specialties.

**Table 2.1**

**Neurogenetic molecular tests available through the UK genetic testing network (simplified list; the network website should be consulted for details, since these are likely to change rapidly)**

Adrenoleukodystrophy  
Alpha galactosidase A deficiency (Fabry disease)  
Alzheimer disease (familial)  
Battens disease  
CADASIL  
Canavan disease  
Charcot Marie Tooth disease (X-linked)  
Congenital muscular dystrophies  
Congenital myasthenic syndromes  
Dystonia (type 1)  
Emery Dreifuss muscular dystrophy  
Episodic Ataxia Types 1 & 2  
Facioscapulohumeral muscular dystrophy  
Familial amyloid polyneuropathy  
Familial hemiplegic migraine  
Friedreich ataxia  
Hyperkalaemic periodic paralysis & Hypokalaemic periodic paralysis  
Juvenile onset Parkinson's disease  
Lebers hereditary optic neuropathy  
Limb girdle muscular dystrophy  
Lissencephaly  
McArdle's disease  
Menke's disease  
Metachromatic leukodystrophy  
Microcephaly - autosomal recessive  
Mitochondrial disorders  
Myotonia congenita  
Myotubular myopathy, X-linked  
Neuroaxonal dystrophy (Hallervorden-Spatz)  
Neurofibromatosis type 1  
Neurofibromatosis type 2  
Niemann Pick disease (Type C1)  
Oculopharyngeal muscular dystrophy  
Pelizaeus-Merzbacher disease  
Porphyria, acute intermittent  
Progressive Myoclonus Epilepsy type 1  
Proximal myotonic myopathy (PROMM; type 2 myotonic dystrophy)  
Tuberous sclerosis 2  
Von Hippel Lindau disease

**Table 2.2**

Molecular analysis for neurogenetic disorders; 'core disorders' covered by most UK centres

Duchenne/Becker muscular dystrophy  
Myotonic dystrophy (type 1 mutation)  
Huntington's disease  
Spinocerebellar ataxias (limited range)  
Spinal muscular atrophy (proximal types)  
Charcot Marie Tooth disease

### 3. GENETIC DIAGNOSIS IN NEUROLOGICAL DISORDERS

1. The application of genetic knowledge and technologies is now an essential part of diagnosis in many areas of neurological and genetics practice. These applications may be clinical or laboratory in nature.

#### A. Clinical diagnostic Issues

2. In Paediatric Neurology practice, a high proportion of the major disorders referred prove to have a primary genetic (commonly single gene) basis. This applies both to childhood brain disorders, developmental or neurodegenerative, and also to neuromuscular disorders, including muscular dystrophies and spinal muscular atrophies. A full knowledge of the range of inherited childhood neurological disorders is essential for all Paediatric Neurologists.

3. In adult Neurology, the proportion of primary genetic disorders is less but still considerable, particularly movement and neuromuscular disorders. Expertise in recording family details and knowledge of the particular features of these genetic conditions is essential if they are to be distinguished from the larger number of patients whose disorder does not have a primary basis.

4. For Clinical Geneticists, genetic counselling referrals relating to neurological disorders form a major proportion of the workload, while puzzling and undiagnosed familial conditions are frequently referred to them for diagnosis, especially those with a syndromic or developmental element. Clinical geneticists thus need to be familiar with the clinical as well as genetic aspects of inherited neurological disorders.

5. While all neurologists and clinical geneticists are likely to encounter neurogenetic disorders, the large number of conditions, individual rarity, frequently confusing clinical features, and need for specialised confirmatory investigations, increase the importance of specialist neurogenetics clinics in diagnosis, and for consultants with special expertise, both adult and paediatric, usually based in tertiary centres.

6. Existing clinics (see Section 2) are commonly held jointly between a neurologist and geneticist and may be either generic in nature or for particular forms of neurogenetic disease (eg: neuromuscular disorders, movement disorders). As already stated, these clinics vary in their remit from being entirely diagnostic to offering ongoing clinical management.

B. Laboratory aspects

7. A high proportion of single gene neurological diseases are now amenable to molecular genetic analysis as part of primary diagnosis. Indeed, in many situations DNA analysis has superseded other testing modalities as the method of choice for precise diagnosis, and is the only way that predictive or carrier testing can be offered to other family members. Molecular cytogenetic techniques (FISH) also have a significant role, as may chromosome analysis in neurodevelopmental disorders. However, while DNA analysis allows a common technology to underpin the analysis of genes for widely different diseases, it is often important for genetic and biochemical analysis to be closely linked, as for example when a number of different gene mutations may underlie a particular phenotype. Here the use of other investigations prior to genetic testing will significantly improve the yield and efficiency of the DNA analysis performed. These situations may be very complex and rely on a multidisciplinary approach to diagnosis which should come from services with particular expertise in this area.

8. A limited range of core molecular tests is available in all NHS genetics laboratories. These represent not only the more common neurogenetic disorders but also those where molecular testing may be relatively straightforward, either because all or most cases of a condition will involve changes in a single gene, or because there is a single mutation type involved. The relative rarity of many disorders, together with additional complexity in the application of molecular tests, has led to the establishment of the UK Genetic Testing Network, involving all UK centres to give a wider range and more equitable use of tests by a collaborative arrangement (see Tables 2.1 and 2.2). We strongly support the establishment and further development of this Network. In recognition of the specialised and at times multidisciplinary nature of diagnosis in these disorders, the National Specialist Commissioning

Advisory Group (NSCAG) has designated a diagnostic and advisory service for four groups of rare neuromuscular disorders.

9. Currently, however, the mutations found to be responsible for many of the rarer neurogenetic disorders, are only analysed in research laboratories, either here or abroad, with aspects of quality control and clinical utility often uncertain. In addition, inherent in this situation is a great deal of inequity of access, as individual clinicians may or may not be aware of a research laboratory interested in receiving samples. When research projects end, there is often no facility in the NHS or elsewhere to undertake these analyses as a service. It is hoped that the UK Genetic Testing Network and the recently established National Reference Laboratories will help to resolve this problem. However, the extreme rarity of some of the disorders may in fact indicate that a European solution to this problem, with designated laboratories serving more than one country would be a more realistic one from the point of view of establishing and maintaining expertise.

10. Molecular genetic analysis was originally used mainly by clinical geneticists, but is now widely used by Neurologists (adult and paediatric) as part of diagnosis, alongside imaging, electrophysiological, biochemical and histopathological tests. It has already been shown that molecular analysis may reduce or even replace these other forms of test, often more invasive, in particular circumstances. Further Health Service Research will be important to provide firmer evidence on this.

While this situation is clearly of benefit to many patients in reducing the need for invasive tests, it is also true that easy access to molecular genetic testing for rare disorders may lead to diagnoses being made that are not fully understood by non-specialists. In some regions this is addressed by there being a “gatekeeper” for specific molecular genetic testing. For example, testing for Huntington’s disease may be requested by neurologists who are investigating a patient with an undiagnosed movement disorder, but the major implications that making this diagnosis would have for the wider family need to be addressed before the testing can be done. Patient organisations such as the Jennifer Trust for Spinal muscular atrophy (SMA), have also expressed concerns that the ready diagnosis of SMA by routine molecular diagnosis means that patients are not being referred to specialised centres and that their management may therefore be compromised. It is quite clear that future

recommendations for neurogenetic services future will need to take these issues into account.

11. The details of service organisation for molecular genetics laboratories are not covered in this report, but it should be noted that, in addition to laboratory accreditation (through CPA) a detailed quality assurance system (NEQAS) exists, including both analytical and interpretive aspects of testing. The current range of available molecular tests for neurogenetic disorders has been given in Table 2.1 in Section 2, while their use in presymptomatic testing and prenatal diagnosis is discussed in Sections 5 and 6.

12. The limited availability of many molecular genetic tests for inherited neurological disorders raises the question of whether their use in diagnosis should be restricted to specialist centres. Evidence from the UK Huntington's disease consortium does not suggest that there is excessive or inappropriate use of such tests in this condition, but it seems wise that for all newly introduced tests any evaluation and audit includes information on specialty of referring clinician, so that use can be monitored.

### Recommendations

3.1 Specialist neurogenetics diagnostic clinics, usually run jointly by a clinical geneticist and neurologist (adult or paediatric), form a valuable activity that supports and enhances both neurology and clinical genetics services. The majority of teaching centres have such a clinic; we recommend that existing clinics are strengthened, supported and formally designated and that they are established where they do not yet exist.

3.2 We recommend that each centre has a designated consultant clinical geneticist and neurologist (involving where possible those with paediatric as well as adult expertise in the field) to take overall responsibility for the running and development of neurogenetics clinics and other clinical services in the field with nurse specialist or genetic counsellor input to ensure ongoing patient support.

- 3.3 Detailed recommendations on laboratory genetics services for inherited neurological disorders are not within the remit of this working group, but we emphasise the importance of these services, their development in a co-ordinated, equitable and effective manner, and that staff involved with clinical aspects of neurogenetics should be closely involved in this process.
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#### **4. GENETIC COUNSELLING SERVICES**

1. This is the area, together with genetic tests, that is most in people's minds when considering genetic services for neurological disorders. Genetic counselling is a complex activity, combining knowledge of genetic mechanisms and risks with clinical and diagnostic skills, together with the ability to communicate information on both risks and the increasing availability of options to avoid these. The use of genetic tests is often linked to genetic counselling, notably in presymptomatic testing and the detection of carriers for autosomal recessive and X-linked disorders.

2. As with most other medical activities, genetic counselling can be considered at several different levels. For most common neurological disorders, as indicated in Section 9, information on genetic risks can mostly be given appropriately by those in primary care and by general neurologists (adult and paediatric), who may be investigating or following patients. Specialist genetic counselling referral may be indicated if the family history or other factors suggest a mendelian sub-type of the disorder (see Section 9) or if there is particular concern within the family.

3. For single gene neurological disorders, which make up a considerably higher proportion of cases than in most other medical specialties, genetic risks will frequently be high and family concern may generate referrals directly among healthy relatives as well as those affected. Here specialist genetic referral is clearly indicated, unless the clinician already involved has both the time and experience required for effective genetic counselling. An exception is probably the group of childhood autosomal recessive disorders seen by paediatric neurologists, where the genetic risk aspects are mainly restricted to the immediate family. All paediatric neurologists need to be aware of the importance of discussing genetic and reproductive aspects at an appropriate early stage.

4. Neurological disorders make up a significant proportion of the workload of all medical genetic services. Families may be large and extended (e.g. HD), inheritance patterns may make it far from obvious which family members are at risk (e.g. X-linked conditions such as Duchenne muscular dystrophy), while risk estimates may be affected by such factors as age-related gene penetrance, parental origin and genetic

heterogeneity. All these are topics with which clinical geneticists will be familiar with from their work with other types of genetic disease.

5. A further advantage that clinical geneticists have in genetic counselling, is that genetic clinics are structured to allow the considerable time needed to listen to and resolve the concerns of those attending, as well as to transmit often complex information. This is greatly helped by the integral involvement of nurse specialists and genetic counsellors as part of the overall clinical genetics service, as well as by the close links between clinical genetics and genetics laboratories. The availability of a network of genetics clinics covering district hospitals but with consultants primarily based in a specialist centre allows considerable geographical equity of service provision.

6. Problems may arise, however, in the handling of neurological genetic counselling referrals in a generic genetic counselling clinic. These may result from uncertainty or difficulties in clinical diagnosis, or in particularly difficult or specialised activities, such as HD presymptomatic testing (see Section 5). It is in areas such as these, rather than in the majority of genetic counselling referrals related to neurological disorders, that specialised neurogenetics expertise is most valuable.

7. Diagnostic neurogenetics clinics, usually involving both a neurologist and a clinical geneticist with special neurogenetics expertise, are especially valuable in clarifying the not infrequent situations where either the clinical diagnosis or the genetic aspects, or both, are particularly problematic (see Section 3). However, disease specific or management related clinics do not always provide an appropriate setting for genetic counselling, though they may be a valuable opportunity for detecting important or unresolved genetic issues.

8. It should be emphasised that the majority of genetic counselling referrals primarily involve not patients themselves but healthy individuals, who are concerned by possible risks for themselves and for existing or future children. This is a further reason why genetic counselling services are generally best based in a setting separate from the conventional medical clinic.

## Recommendations

- 4.1 Most genetic counselling referrals which include a neurological component do not require a specialist neurogenetics service, but are appropriately handled by general medical genetics services or in straightforward situations, by general neurologists and family doctors.
  
- 4.2 A specialist neurogenetics clinic, involving both clinical genetics and neurology staff, is of considerable value in establishing a precise diagnosis in situations of diagnostic uncertainty or rarity, thus allowing an accurate foundation on which genetic counselling can be based. They can also advise on the use of complex pathways of diagnosis which may require the integration of molecular genetic and other testing modalities.

## 5. PRESYMPTOMATIC GENETIC TESTING

1. While imaging and biochemical investigations may show abnormalities in individuals without symptoms, it is only since the development of DNA technologies that the possibility of presymptomatic testing for a wide range of late onset neurogenetic disorders (potentially all) has begun to emerge. The existence of a primary genetic change from conception onwards, independent from the existence of symptomatic disease, is a major conceptual change in medical practice.

2. Initial presymptomatic genetic tests relied on the use of marker genes closely linked to the disease locus and involving the analysis of samples from multiple family members. Now, increasingly, it is possible to use specific mutations, giving a high degree of accuracy in prediction, provided that the gene is fully penetrant in the disorder concerned. The situation for disorders where a specific mutation is only one of multiple factors determining the development of disease is discussed under susceptibility testing, in the section on common neurological diseases (Section 9).

3. Most of our evidence for the best patterns of practice in relation to presymptomatic testing comes from the neurodegenerative dominantly inherited disorder, Huntington's disease (HD); experience of presymptomatic testing for other neurogenetic disorders remains limited, though outside the neurological field there is increasing evidence for familial cancers.

4. Data from the UK Huntington's Prediction Consortium, which has monitored all presymptomatic tests since the outset of testing 15 years ago, with information on over 4,000 completed tests, has given valuable information on the effects of testing and on clinical practice in this field, which are closely in line with the experience of others internationally, in North America and Continental Europe.

5. The main relevant points to emerge are:

- Only 15-20% of those at risk for HD decide to be tested

- The laboratory aspects of testing are now reliable and clear-cut in almost all cases
- A full supporting framework of preparation and counselling is universally used and is welcomed and regarded as important by support groups, professionals and almost all applicants for testing
- Very few severe adverse events after testing have occurred with this practice framework
- Testing issues for individuals are numerous, complex and variable and the close collaboration between the genetic centres benefits both professionals and families alike
- The testing framework also supports other family members who may subsequently become carers or for whom their personal genetic risk has been altered by the test result

6. In the UK (and virtually world-wide) the presymptomatic testing programmes for HD are undertaken almost exclusively by clinical geneticists; programmes are available in all regional genetics centres and there are close links with both Neurologists (especially for those individuals proving to have clinical abnormalities) and also Psychiatrists (particularly for the minority with preceding or current psychiatric symptoms). Commissioning for both the clinical and laboratory aspects of presymptomatic testing currently is through genetics.

Presymptomatic testing for other neurogenetic disorders currently remains infrequent. There are data for ataxias, and for myotonic dystrophy, but figures from the UK HD Consortium show tests for all other neurogenetic disorders together amount to less than 10% of those for HD. Disorders involved include familial prion disorders, CADASIL, familial motor neurone disease and familial Alzheimers. There is general agreement that these few requests can be handled by the programmes for HD presymptomatic testing, with modifications appropriate for the particular disorder. It will be important to continue monitoring the frequency of such requests, since possibilities for therapy could increase demand in the future.

## Recommendations

- 5.1 Presymptomatic testing for late onset neurogenetic disorders (eg for Huntington's disease) is a particularly complex activity, requiring medical genetics and genetic counselling staff with particular experience in this area; it should be recognised as part of specialist neurogenetics activity.

## **6. PRENATAL AND PREIMPLANTATION GENETIC DIAGNOSIS**

### Prenatal diagnosis of childhood neurogenetic disorders

1. Prenatal diagnosis has been an important option for severe childhood brain and neuromuscular disorders for many years. Most such disorders are recessively inherited (some X-linked), giving high recurrence risks in sibs of an affected child. Biochemical analysis allows accurate prenatal diagnosis for many metabolic conditions (e.g. Tay Sachs, Batten's disease) while DNA analysis now makes it feasible for many more (e.g. Duchenne muscular dystrophy, infantile spinal muscular atrophy, lissencephalies). A combination of biochemical and molecular approaches may be needed.

2. Patterns of practice in this area are relatively well established, involving close links between paediatric neurologists, other paediatricians and clinical geneticists at a clinical level; and with both molecular genetics and specialist biochemistry laboratories. The rarity of some of the disorders and the highly specialised laboratory techniques (especially enzyme assays) necessitates these close links, which in general work well. Wherever possible, the possible options and wishes of the family should be fully discussed and relevant molecular tests done prior to a pregnancy.

3. Such problems as do occur are principally related to commissioning (see Section 12) involving questions of access and funding, and emphasising the importance of ensuring support for laboratories undertaking a supra-regional or all UK role. The NSCAG scheme for neuromuscular disorders, the supraregional enzyme assay service and the UK genetic testing network are examples of such networks, whose value is of general importance, not just for prenatal diagnosis.

### Prenatal diagnosis of adult neurogenetic disorders

4. While much less frequently requested than in childhood disorders, molecular genetic analysis is now equally possible prenatally as in postnatal life. Most data come from HD, where UK figures show requests to be rare (around 10% of the

frequency for presymptomatic tests) but important for those requesting them. Prenatal testing for myotonic dystrophy is principally related to the risk of the severe childhood form. Experience with prenatal testing for other adult neurogenetic disorders is extremely limited.

5. Current practice for HD prenatal diagnosis is for this to be handled as part of the overall service for genetic counselling and predictive testing, with clinical geneticists primarily involved. Since all these aspects are closely inter-related, and may indeed arise simultaneously, this pattern of practice appears to be appropriate; almost no neurologists or obstetricians have expressed a wish to take a lead role in this area.

#### Pre-implantation genetic diagnosis (PGD)

6. Despite extensive publicity, experience in this field remains very limited, in the UK as elsewhere. Licensing arrangements are the responsibility of the Human Fertilisation and Embryology Authority. For neurogenetic disorders there is UK experience for infantile spinal muscular atrophy, with preliminary data for HD, myotonic dystrophy (greater experience for these is available from Continental Europe) and sexing for X linked neurological disorders. There are currently six centres licenced by the HFEA to practise PGD.

7. IVF centres have, in the past, often failed to link closely with genetic services, but now closer cooperation is developing, allowing fuller information for families on the advantages and limitations of this approach. A recent DOH document has outlined interim recommendations for good practice in this field, applying to neurogenetic disorders as much as to others. It suggests that PGD referrals should first be seen by clinical genetics services, to avoid unnecessary or inappropriate referrals and to ensure that the diagnosis made in the family is accurate. This also allows experts in both disciplines to plan jointly future strategies for PGD for new genetic disorders.

8. It seems likely that demand for pre-implantation diagnosis will remain as a rarely used, though important option for families with inherited neurological diseases,

though the situation could change if there are major improvements in IVF success rate and equity in health service funding for PGD across the UK. For the present it is preferable for it to remain localised in a very small number of expert centres, so that they can gain satisfactory experience; equitable arrangements for access through the NHS across the UK need to be reinforced. Neurogenetic disorders do not currently need special or separate arrangements.

### Recommendations

- 6.1 Prenatal diagnosis of childhood neurological disorders requires close liaison between paediatric neurologist, clinical geneticist and the specialised laboratories (both genetic and biochemical), needing to be involved in this complex group of rare disorders.
- 6.2 Prenatal diagnosis for serious adult neurogenetic disorders is an uncommon but important option for families. It is best handled in conjunction with discussions of presymptomatic testing and by the same specialist staff, linking with fetal medicine services.
- 6.3 Pre-implantation diagnosis remains a very limited service requiring both a high degree of expertise in testing for the particular disorder and close links with clinical genetics services. Neurogenetic disorders do not currently need specific arrangements, but specialist neurogenetic services need to be fully informed of current and emerging possibilities in this field so that their patients have access to these services if required.

## **7. MANAGEMENT AND THERAPY FOR INHERITED NEUROLOGICAL DISORDERS**

1. Although treatment of inherited disorders may not seem strictly to form part of genetic services, in the case of inherited neurological disorders the links are so close as to require full discussion here. In practice, not only neurologists but clinical geneticists with a special interest in neurogenetics are extensively involved with management and therapeutic aspects. These existing links provide a valuable foundation on which further therapeutic initiatives can be built.

2. A wide range of different types of management and therapeutic approaches exists, outlined in table 7.1. At present, few of these can be regarded as curative, though this is starting to change; the practical management issues are often complex, with many issues specific to the individual disorder and some requiring involvement of other specialists (e.g. cardiologists, ophthalmologists).

3. Specific management clinics have been set up for a series of inherited neurological disorders, as indicated in table 2.1 in Section 2, while HD and neuromuscular disorders are the most prominent and widespread; specialist management clinics also exist in a few centres for disorders such as neurofibromatosis, tuberous sclerosis and ataxias. Some are multidisciplinary, involving such fields as occupational and physiotherapy (neuromuscular disorders) and psychiatry (HD).

4. Clinical geneticists have played a major role in initiating some of these management clinics, partly because, until relatively recently, management was not seen as a high priority for neurologists; partly because of the broad clinical background and expertise of some clinical geneticists and their familiarity with the problems of specific conditions.

5. Currently, most clinics involve both a neurologist (adult or paediatric) and a clinical geneticist with specific expertise working closely together, often with nurse specialist or other professional involvement; however the pattern is extremely variable

in centres across the UK as found in the survey (Section 2). The lack of recognition for neurogenetics as a defined subspecialty area may give practical difficulties in obtaining funding, supporting staff and suitable clinical space for clinics, particularly since the field is unlikely to be high on the agenda of most host trusts. Many patients will be coming from a wide geographical area; this may also give organisational difficulties. A wide catchment area is likely to be essential if a clinic is to maintain a critical mass of referrals and expertise.

6. Where specific therapies, drug or dietary, are possible, patients may be treated in regular neurology clinics, but this is relatively unusual, since the disorders are rare and may be unfamiliar to most neurologists, while therapies may be experimental and need close monitoring. With the prospect of new agents requiring clinical trials, these are most likely to be feasible in the context of specialist clinics, often those already offering regular assessment and more general management, along with clinically orientated research on the condition.

7. Genetic disease support groups have an important role in promoting, and in some cases funding, specialised management clinics, such groups clearly seeing the contrast in quality of management between these and management in general clinics, as well as the geographical inequities that currently exist.

8. If clinics for management and therapy of inherited neurological disorders are to develop in scope and geographical coverage, and are to be able to evaluate and deliver new therapeutic advances, then the present foundations, largely ad hoc and often insecure, must be strengthened. The existing close cooperation between neurologists and geneticists in this would be considerably enhanced if the field of Neurogenetics is recognised as a subspecialty, so that those practising it, whether from Neurology (adult or paediatric) or genetics, can gain full recognition for their work in relation to clinics for management and therapy of inherited neurological disorders.

## Recommendations

- 7.1 Management of many neurogenetic disorders is frequently complex, with aspects specific to individual disorders or disease groups, giving considerable benefit from specific management clinics led by staff with specialised neurogenetics expertise.
- 7.2 Specialised neurogenetics management clinics require clearly designated organisation, staffing, funding and support. Multidisciplinary involvement is frequently needed.
- 7.3 These clinics should form part of the recognised remit of Neurogenetics and involve co-operation between Neurology and Genetics services.
- 7.4 Clinics may appropriately serve patients from a wide geographical area and may need to do this to give critical mass of experience. Geographical equity across the UK is an important consideration in planning these specialised clinics and strengthening and properly supporting those that already exist.

**Table 7.1**

**MANAGEMENT AND THERAPY OF INHERITED  
NEUROLOGICAL DISORDERS**

Management

Assessment and help for physical disability  
Assistance with social aspects  
Monitoring for systemic complications (which may be multisystemic)  
Information and support  
Recognition of genetic issues

Therapy

Symptomatic drug therapy (e.g. for somnolence in myotonic dystrophy;  
psychiatric problems in HD)  
Specific drug therapy (e.g. ion channel disorders)  
Specific dietary therapy (e.g. inherited metabolic disorders)  
Enzyme therapy (e.g. lysosomal disorders)  
Cell implantation (experimental)  
Organisation of trial frameworks

## **8. THE PATIENT AND FAMILY PERSPECTIVE**

1. The perception of and priorities for genetic services held by patients with neurological disorders and their relatives are not necessarily the same as those of professionals. When developing services it is thus essential to have as extensive consultation with patients and their representatives as possible and for this to be included from the outset.

2. A wide range of lay societies and patient support groups exists for neurological disorders, both in the UK and internationally, forming an important and influential grouping that increasingly is listened to direct by policy makers and government.

3. Groups representing inherited neurological disorders have the problem of relative rarity by comparison with societies involved with commoner disorders (such as epilepsy or MS). This may give financial and organisational limitations and has resulted in over 100 UK associations forming the joint body Genetic Interest Group (GIG) to give more effective influence. Many of its member societies are responsible for inherited Neurological disorders.

4. General issues of particular concern to support groups for inherited neurological disorders include:

- Availability and equity of access to genetic services
- Geographical convenience of clinics
- Excessive waiting times for appointments
- Inconsistency of referral by clinicians
- Quality and expertise of specialist staff
- Provision of clear written information
- Availability of specialist management clinics
- Adequate auditing of services

GIG have published a document summarising the main areas that a genetics service should cover if it is to provide a high quality service. The Royal College of Physicians has also published guidelines on this.

#### The direct role of support services

5. Increasingly support groups for inherited neurological disorders are playing an active role in ensuring that patients (not just support group members) receive high quality management. Key areas include:

- Written information and leaflets on different aspects of the condition, increasingly available via the Internet.
- Details of appropriate specialist services available in particular areas
- Group meetings for social contact and support
- Professional workers directly employed by the groups, allowing more detailed assessment of needs.
- Pastoral support for carers

6. This last field is of particular importance for disabling inherited neurological disorders (e.g.: Huntington's disease, muscular dystrophies), where patients may need to access a wide range of health and social services, and where a worker focussed on a particular disorder may have valuable specific experience not available to more generic staff employed by the NHS or social services. Some of these staff may be located in specific neurological and genetics services; in other situations the patient association may provide the funding for an NHS based nurse specialist or other professional.

#### Recommendations

8.1 Management of many neurogenetic disorders is frequently complex, with aspects specific to individual disorders or disease groups, giving considerable benefit to specific management clinics led by staff with specialised neurogenetics expertise.

- 8.2 Specialised neurogenetics management clinics require clearly designated organisation, staffing, funding and support. Multidisciplinary involvement such as physiotherapy and occupational therapy is frequently needed.
- 8.3 In most instances, such clinics will form part of a designated neurogenetics service.
- 8.4 Clinics may appropriately serve patients from a wide geographical area and may need to do this to give critical mass of experience. Geographical equity across the UK is an important consideration in planning these specialised clinics.

## **9. GENETIC SERVICES AND COMMON NEUROLOGICAL DISORDERS**

1. Almost all the aspects of genetic services described in the previous sections have related to simply inherited disorders, where the genetic basis plays the predominant (though not exclusive) role in the development of disease. While individually rare, these amount in total to a considerable body of serious, chronically disabling and often fatal disease, more conspicuous in Neurology than in most other specialties.

2. By contrast, most common neurological disorders do not follow simple patterns of inheritance and are the result of multiple factors, still mostly unknown. Although new gene mapping advances are beginning to identify some of the genetic components, this is proving much more difficult and complex than some originally thought likely. The identification of genetic susceptibility factors is thus in most cases still a long way from scientific clarity, and even further from use in clinical practice.

3. An important exception lies in the existence within most common disease groupings of rare subsets showing mendelian inheritance, essentially equivalent to other single gene neurogenetic disorders, but without clearly distinguishable identifying features. Table 9.1 lists some of these in relation to their broader parent group.

4. The recognition of such sub-groups is important for both genetic and overall management. It may be feasible by careful clinical assessment (e.g. tuberous sclerosis as a cause of epilepsy, Kennedy's disease as a subset of motorneurone disease), but is increasingly helped by availability of molecular diagnostic tests. However, since these are often not easily available, their use in the context of common disorders needs to be selective and cautious; in contrast to cancer genetics, where clear guidelines exist for identifying comparable subsets in breast and colorectal cancer, no systematically collected evidence exists for common neurological disorders as to when the use of molecular analysis is effective and appropriate.

5. Leaving aside mendelian subsets (and their equivalents resulting from mitochondrial gene mutations), there is currently no evidence that molecular genetics testing plays any valid service role at present in the diagnosis of common neurological disorders, nor in determining who is susceptible to them. Considerable further evidence will be required before this changes; apart from any scientific validation, a careful assessment will be needed of whether detection of relatively small increases (or decreases) of genetic risk for common disorders is of benefit; this is especially relevant to any potential proposals for widespread population screening or testing of relatives.

6. Since the investigation and management of common neurological disorders is principally at the primary and secondary care levels, and is unlikely to involve directly those with a specialist neurogenetics remit, it will be important for clear information and guidelines to be developed as to how medical and other staff should handle genetic enquiries related to these common disorders. Clearly it is important that genetics services (laboratory or clinical) should not be swamped by inappropriate samples or patient referrals; at present, there is no evidence that this is happening, but the situation could change rapidly.

7. Information on genetic risks to relatives (which are generally not greatly increased) is available for a number of common disorders and can usually be given as appropriately by generalists as by specialists in clinical genetics or neurogenetics. Awareness of factors (e.g. family history or unusually early age at onset) that might suggest a mendelian subset, is important in allowing there to be distinguished and referred appropriately.

8. Where concerns exist specifically regarding genetic risks, referral to general genetics services will normally be appropriate. Some neurological services, e.g. epilepsy clinics, are also particularly well placed to provide genetic risk information, along with information on teratogenic risks.

### Recommendations

- 9.1 Specialist neurogenetics services currently have only a minimal role in relation to common neurological disorders, a situation unlikely to change in the near future.
- 9.2 A small but important specific area requiring awareness, recognition and specialist referral is that of the uncommon single gene subset of families occurring within a much larger grouping of a common disorder.
- 9.3 Clear and accurate information on genetic risks needs to be available for general neurologists and family doctors, to allow them to respond to patient enquiries and avoid inappropriate referrals.
- 9.4 Molecular genetic tests have no validated service role at present in testing for susceptibility to common neurological disorders, unless a rare mendelian subtype is suspected.

**Table 9.1**

**MENDELIAN SUBSETS IN COMMON NEUROLOGICAL DISORDERS.**

**Examples**

<u>Common Disease Grouping</u>	<u>Mendelian Subset</u>
Stroke	CADASIL
Epilepsy	Several rare ion channel disorders
Brain tumour	Neurofibromatosis, tuberous sclerosis
Motorneurone disease	Familial motorneurone disease due to superoxide dismutase deficiency; Kennedy's disease
Alzheimer's disease	Familial Alzheimer's due to presenilin gene mutations
Parkinson's disease	Familial juvenile Parkinson's

## 10. TRAINING

1. Training of medical staff in neurogenetics needs to be considered at different levels: primary care; consultants in general neurology, paediatric neurology or clinical genetics; and specialists in neurogenetics.

### 2. Training for Primary care staff

As noted earlier, a high proportion of inherited neurological disorders, including most for which genetic services are currently relevant, follow single gene inheritance and are relatively rare – many family doctors will have at most only one or two families with a particular condition in their practice, while they may never encounter some of the rarer ones during a lifetime.

3. For this reason, it is preferable that in both undergraduate and general professional training an emphasis is placed on general principles, rather than on details of specific disorders. Important aspects for all staff in primary care include:

- Awareness of the importance of family history and recognition of the basic inheritance patterns.
- A general knowledge of which groups of neurological disorder are likely to have a primary genetic basis.
- Knowledge of genetic services in the particular area and willingness to refer, particularly when genetic risks are likely to be high.
- Awareness that healthy relatives may be at risk and should be offered access to genetic services.
- Appreciation of the importance of support groups and other sources of information.

### 4. Consultant adult neurologists; paediatric neurologists and clinical geneticists who do not have inherited neurological disease as a special interest or expertise

Adult neurology and clinical genetics share a comparable structure in that most consultants have both a subspecialty area of expertise and also have generic responsibilities in their specialty, with the latter often based in district hospitals.

Paediatric neurologists likewise hold district based clinics, though their main base is generally in teaching centres.

5. In their district based role, consultants will encounter a considerable number of referrals involving neurogenetic disorders, even though this may not be their primary interest. The proportion which they refer on will vary, but a considerable proportion will be dealt with at this level, so training needs are significant. This is perhaps especially important for paediatric neurologists, all of whom will inevitably meet a large number of genetic conditions in their practice.

6. The survey described in Section 2 found little evidence of systematic training in neurogenetics, either for neurologists or clinical geneticists. However, clinical genetics trainees have a requirement to experience genetic counselling and testing in relation to HD, and also rotate through different clinics, ensuring a basic familiarity with the field. This will rarely include aspects of clinical diagnosis, however; while correspondingly trainee neurologists will not usually be exposed to the patterns of 'genetic practice' involving genetic counselling and related issues.

7. Most training programmes in adult and paediatric neurology and in clinical genetics have specific shared day courses at supra-regional level, that could be utilised as a foundation of knowledge in neurogenetics and supplemented by an annual more extensive course (see below).

8. Training for specialists in neurogenetics

This demands a considerably higher level of training, both in investment of time and in the construction of specific programmes of work and study. The survey found only three centres with specific neurogenetics trainees and all were occupying research fellowships, with a lesser emphasis of training related to services. The centres in Newcastle and at Queens Square account for most of these posts.

9. Currently, there are no designated NHS training posts either in neurology or genetics that have neurogenetics as a specific emphasis or focus. Although most centres considered they were able to give some experience in the area, this was not felt to be adequate for trainees hoping to make it their main subspecialty interest.

10. Trainees, whether clinical geneticists or adult or paediatric neurologists, will be unlikely to consider neurogenetics as a career unless there are clearly defined training schemes and also the possibility of consultant level posts. Current staff at trainee level may be able to obtain experience through clinical research fellowships, especially those aiming for an academic career (see Section 11), but this is no substitute for service orientated clinical training.

11. The unmet needs of trainees with a background in neurology will especially be in genetics; conversely for those coming from genetics the need will be mainly in clinical neurology and related neurosciences. Fortunately, the range of activities already existing in most centres and the close links between genetics and Neurology, make this more a task of coordination and development of programmes, rather than of initiating completely new activities.

12. The working group has suggested the following activities as important elements in specialist training. Although training programmes in adult and paediatric neurology are largely distinct, these points apply equally in principle to both fields.

1. Access to clinics in neurogenetics with attendance at clinical discussion meetings etc.
2. Additional needs – ‘bridging the gap’ between the disciplines:
  - a. Neurologists might need training in practice or predictive and prenatal testing protocols, result giving, liaison with genetic nurses, obstetric services etc
  - b. Geneticists might need exposure to the diagnostic routes in neurological diagnosis, neurophysiology, Neuroimaging, neuropathology (including muscle pathology/immunocytochemistry)
  - c. Either might benefit from training and exposure to Cancer genetics, particularly with respect to such disorders as neurofibromatosis and Von Hippel Lindau disease
3. The above might be largely addressed by sabbatical periods, fellowships or exchange of trainees between disciplines.

13. Finally, an annual neurogenetics conference, aimed at trainees, would be a valuable experience for both specialists and general trainees in neurology and clinical geneticists, as well as for consultants whose previous training may not have covered the field adequately.

### Recommendations

- 10.1 Family doctors need to be familiar with the broad principles of genetics in relation to inherited neurological disorders, rather than the details of individual rare conditions. They also need to be familiar with and use appropriately the specialist services in their area.
- 10.2 General neurologists, in particular paediatric neurologists, need a significant exposure during their training to the genetic issues posed by inherited neurological disorders, while trainees in clinical genetics will benefit from familiarity with the clinical aspects of these disorders. Specific shared training days at supraregional level should help with this.
- 10.3 Specific and detailed training programmes need to be established for those geneticists and for adult and paediatric neurologists aiming at a career in neurogenetics. Such programmes should be shared between the parent specialties; there already exists a wide range of activities for them to be based on, but this requires extending and defining more clearly.
- 10.4 An annual national neurogenetics training meeting is suggested as a specific event for trainees across the UK, including genetic counsellors specialising in this field.
- 10.5 There are currently no NHS training posts specifically or even partly designated in relation to neurogenetics. These need to be created (either within the existing complement or as additional posts) in each teaching centre providing specialist genetic services for neurological disorders. Initially they should be based in centres with particular expertise and rotation could be

arranged to maximise experience. They should be open to trainees in either clinical genetics or neurology (adult or paediatric).

- 10.6 Consultant posts with neurogenetics as a defined subspecialty, in both clinical genetics and neurology (adult or paediatric), will be essential if doctors are to take up training posts in the field.

## **11. RESEARCH AND ACADEMIC ASPECTS**

1. Research into genetic aspects of neurological disease has a long and distinguished tradition, extending back even before the rediscovery of Mendel's principles of inheritance a century ago. The work of British neurologists and geneticists has made central contributions to our genetic understanding of such disorders as the muscular dystrophies, ataxias and Huntington's disease, and has been in the forefront of the mapping and isolation of the genes involved.

2. Research into inherited neurological disorders is actively pursued in a number of clinical UK academic centres, with an increasing emphasis on the possibilities for prevention and therapy. Recently, it has extended to the analysis of the genetic factors involved in common neurological disorders. Basic genetic research, including the use of model organisms, is likewise proving to be of direct relevance to our understanding of human neurogenetic disease.

3. The lack of clearly defined NHS structures for genetic services for neurological disorders has meant that the existing clinical academic units are not only the focus of research in this field, but that the services are also largely based around clinical academic staff and have been developed in this context. Likewise, almost the only opportunities for training in neurogenetics are in the form of research training fellowships (see Section 10).

4. This unbalanced situation is not only disadvantageous to the development of NHS services, but it also hinders academic work, since there is a lack of securely established and funded clinics and other services on which research can be based. Current research related clinics are frequently dependent on research grants or charities funding and may be vulnerable to the loss of a specific senior research worker. Thus a strengthened service framework for inherited neurological disorders, and an overall UK pattern for genetic services for neurological diseases, will directly benefit research and other academic activities in this field.

5. Since research and service developments in the area are extremely closely related, often involving the same senior staff, there is a strong case for encouraging both, if a secure foundation for neurogenetics is to be established in the UK. Possible approaches to this include:

1. Recognition of neurogenetics as a subspecialty within both neurology (adult or paediatric) and clinical genetics, and promotion of consultant posts with this remit. This would encourage those in research training posts to remain in the field at NHS consultant level, even if a permanent academic post is not available.
2. Designation of neurogenetics within NHS training posts (see Section 10). This would facilitate movement of trainees between research training fellowships and NHS training posts without loss of the interest and expertise they have acquired.
3. Creation of a common core of teaching activities relevant to both research and NHS training posts. As indicated in Section 10, this could largely be achieved by bringing together existing activities at regional and UK level.
4. Encouraging links with research and NHS laboratories to facilitate clinically orientated research projects.
5. Appropriate academic recognition and protection of academic time for senior NHS based staff, providing neurogenetic services who are also research and academically active.

6. At an academic level, there is a need for strengthening of links between the different centres involved with clinical neurogenetic research. This would be especially valuable given the dispersal of clinical research staff and lack of critical mass outside a very small number of centres such as National Hospital Queen Square and (for neuromuscular disorders) Newcastle. It has to be recognised that a factor working against this is the diversity of inherited neurological disorders (e.g. neuromuscular as compared with brain degenerations), which inevitably tends to encourage fragmentation and isolation. However, the numerous shared core factors outlined above and the rarity of most specific diseases or disease groups, makes it important for the field of neurogenetics to be considered as a whole, not simply as its numerous constituent parts.

7. In summary, clinical academic staff are at present playing a key role in service provision and training, but are unsupported by a clearly defined NHS structure. Provision of this should strengthen the academic field of neurogenetics, as well as removing the fragility of those current services with an academic basis.

### Recommendations

- 11.1 Research and other academic activity in relation to genetic aspects of neurological disease is of high quality in the UK, but is hindered by the lack of clearly defined and supported NHS clinics and other facilities for neurogenetics services.
- 11.2 Current research training posts in neurogenetics should include elements of service-related training posts. Research and NHS training posts should be constructed to allow movement between each type of post so as to give flexibility in pursuing an NHS based or academic consultant career.
- 11.3 Specialist neurogenetics clinics (both diagnostic and management) offer considerable potential for the understanding and better therapy of uncommon neurogenetic disorders and should be planned and staffed to facilitate these developments.
- 11.4 Creation of specific clinical academic posts in neurogenetics, preferably joint or closely linked between the parent specialties, will have an important role in promoting development of the field and encouraging able people to enter training in it, as will academic recognition of senior NHS staff already in the field.

## **12. ORGANISATIONAL ASPECTS: STAFFING, RESOURCES AND COMMISSIONING MECHANISMS**

1. Based on the existing activities and suggested improvements outlined in previous sections, it is possible to consider the various organisational changes needed if genetic services for neurological disorders are to progress from their present informally structured and ad hoc arrangements to a high quality, secure and specifically recognised service that will allow consultants to practice satisfactorily and trainees to be attracted to it. The changes needed can be considered at the three levels already discussed, essentially those of primary care, district hospital services and specialist services for neurogenetics.

### **2. Primary care**

Unless major and unexpected developments occur in relation to genetic aspects of common neurological disorders, no radical change in patterns of practice is required. As emphasised in Section 10, education in relation to the main principles relating to genetic disease, awareness of family history, recognition of high risk groups and knowledge of genetic services and how best to use them, are the main points.

### **3. District based and general neurology services**

Most general and paediatric neurologists will have a clear picture of which neurogenetic diagnoses they can confidently make and the range of genetic tests available to help in this. With numbers in the specialty small and most consultants working in both district and teaching centres, there is already likely to be familiarity with and selective referral to those clinical geneticists and neurologists holding specialised neurogenetic diagnostic and management clinics.

### **4. Clinical genetics**

Clinical geneticists without a specific neurogenetics interest will likewise be able to handle most genetic counselling referrals, and again, will have close links with colleagues in genetics and neurology providing specific neurogenetics services. They will also make considerable direct use of laboratory genetics services.

Again, at this level, no major organisational changes are required, but the training needs for both general neurologists and clinical geneticists are significant.

5. Tertiary level services – clinical geneticists and neurologists (adult or paediatric) with neurogenetics as a major field of practice

It is at this level that organisational changes are needed, largely because until now, there has been no clear or uniform pattern of organisation or support for these services, even though they may appear well developed in individual centres. The main steps needed initially include:

1. Recognition of neurogenetics as a specific sub-specialty open both to appropriately experienced clinical geneticists and to neurologists (adult and paediatric). It should be stressed that a full specialty status is not necessary or desirable at present, though this should not preclude some individuals at consultant level dedicating most of their time to the field.
2. Corresponding recognition of neurogenetics in the NHS training structures of both clinical genetics and neurology (both adult and paediatric), along the lines outlined in Section 10.
3. Specific designation of existing clinics and related consultant and support staff activities in this area to give a coordinated service framework for clinical neurogenetics services, including without bias both those primarily based in neurology and those based in clinical genetics.

6. Staffing aspects

The working group survey identified that most teaching centres already had a clinical geneticist and neurologist recognised as having particular expertise in neurogenetics; if formalised and appropriately supported, this should provide firm foundations for further development. Given the different needs and age groups of different groups of inherited neurological disorders for management (e.g. neuromuscular disorders and brain degenerations), it is likely that more than one neurologist may need to be involved in any overall programme of services.

7. At non-consultant level, associate specialists play a valuable role in specific clinic fields in some centres, while nurse-specialist and genetic counsellor support is an integral part of both genetic counselling and specific genetic disease services.

8. It is difficult to estimate the need for new posts, whether consultant or other, until the existing activities are formally recognised, but at the minimum, each centre serving a population of 1-2 million, will require one consultant from clinical genetics and one from neurology, each devoting a substantial part of their time to practice, service development, education and research in the field. Since most regional genetics and neurology specialist centres now have around 5-8 consultants, it should be feasible to designate one such post in each team as having specific responsibility for neurogenetics, or if there is no suitably experienced person, to plan for this in forthcoming appointments. Although the number of paediatric neurologists in the UK is currently small, designation of neurogenetics as a field of activity would be an appropriate part of the proposed expansion in the field.

9. Resources

Rather than suggesting specific additional funding at the present, we suggest that existing activities are fully costed so that the current cost of neurogenetics services to both genetics and neurology budgets can be fully identified. At present, most costs are hidden or not specifically recognised. Accurate costing of staff and facilities would be a necessary preliminary step to any additional recommendations and would complement the recognition of neurogenetics as a defined subspecialty.

10. It is likely that such an exercise will also highlight differences between centres, though any national role of particular centres will need to be distinguished from their regional commitment.

11. Commissioning mechanisms

These may vary in different parts of the UK. There is now agreement on the exact definition of specialised services – at least in England. Genetic services are clearly so designated, but this is only partly the case for adult neurology services, while paediatric neurology is commonly commissioned as part of general child health services. It would seem clear that all the specific neurogenetics services at tertiary level discussed in this report represent true specialist services and should be commissioned as such. This can be achieved within the existing framework, provided that it is recognised that (a) activity carried out within neurological or paediatric

neurological departments is explicitly designated as part of the definition of specialised neurological (or paediatric) services and (b) activity carried out within genetics departments is explicitly flagged as neurogenetics as distinct from general genetics or cancer genetics activity.

#### Laboratory genetics services for neurological disorders

12. The working group has not attempted to address the organisational aspects of these; while usually closely linked professionally to clinical genetics services and commissioned together in most instances, they mostly have a separate management structure within laboratory services of teaching hospital trusts, while some are based within university structures.

13. Given the different responsible bodies from clinical services in terms of Royal Colleges and professional societies, it does not seem appropriate for this working group to make recommendations, other than that close links are required at all levels. The considerable extension in range of molecular diagnostic tests likely to result from the newly formalised UK genetic testing network will be of real benefit to all clinicians involved with inherited neurological disorders.

#### Recommendations

12.1 At primary care level, no major organisational, staffing or commissioning changes are needed, since until service implications arise in relation to common neurological disorders, impact at this level will be slight. There will be a small cost for the educational aspects and practice guidelines recommended.

12.2 No significant changes in organisation are recommended at secondary level, in relation to general adult and paediatric neurologists and clinical geneticists. Training implications will have a specific cost that will need to be shared between clinical genetics and Neurology training budgets and which will have time implications for senior specialist staff.

- 12.3 The principal recommendations of this report are at tertiary level and rest on the recognition of a specific subspecialty (but not full specialty) of clinical neurogenetics within the NHS. That subspecialty should have the remit to provide specialist genetic services for neurological disorders, together with a co-ordinating and educational role in this field extending to secondary and primary care. The commissioning implications are that within the genetics, neurological or paediatric specialised services definitions, activity in neurogenetics should be explicitly recognised as coming within those definitions.
- 12.4 Any recognised subspecialty of clinical neurogenetics should be open to appropriately trained and experienced clinicians whose primary specialty is either clinical genetics, adult or paediatric neurology.
- 12.5 The satisfactory development of this subspecialty will require the active co-operation of the parent specialties, probably through a specific committee and involving the appropriate specialist societies.
- 12.6 The specialist activities of consultants currently working in the field should be specifically designated and recognised within existing commissioning mechanisms, so as to avoid these services being lost with retirement or movement of senior staff.
- 12.7 Where existing services are absent or deficient, creation of new consultant posts, or allocation within an existing complement, should be undertaken to fill these deficiencies.
- 12.8 As a minimum, for a population of 2 million, we recommend that there is one designated post (or full time equivalent) based within clinical genetics and one based in neurology (either adult, paediatric or in combination) to provide consultant leadership. It may be appropriate for this staffing to be shared between consultants with different specific expertise (eg: neuromuscular and CNS disorders, paediatric neurology and adult neurology).

- 12.9 The role of specialist neurogenetics consultants should include not only the running and development of specialist neurogenetics clinics (diagnostic and management) and the development of guidelines for non specialist staff at secondary and primary care levels, but a more general educational and coordinating role in the development of the field, as well as involvement in audit and in research.
- 12.10 Specialist neurogenetics clinics will require definition of support required in terms of both staff and facilities. In particular, the role of nurse specialists/counsellors will be a valuable resource in those areas not specifically requiring a medical training, including specific aspects of genetic counselling and management.
- 12.11 The majority of the above recommendations can, at least in part, be implemented by the specific recognition and utilisation of existing staff and their activities. It would be unwise to estimate additional costs until this first step has been taken.

## APPENDIX

### GENETIC SERVICES FOR NEUROLOGICAL DISORDERS

#### MEMBERSHIP OF WORKING GROUP

Core group (as nominated by Association of British Neurologists and Clinical Genetics Society):

Peter Harper (Chair)	Cardiff
Kate Bushby	Newcastle
Susan Huson	Oxford
Nick Wood	London
Mary Davis	London (Laboratory Genetics)
Simon Hammans	Southampton (Adult Neurology)
Alison Lashwood	London (Genetic counselling)
Daniela Pilz	Cardiff (Paediatric Neurogenetics)
Margaret Read	Former Secretary, CMT, UK (Charcot Marie Tooth Disease)
Raj de Silva	Romford (Adult Neurology)
Sheila Simpson	Aberdeen (Adult Neurogenetics)
Sarah Tabrizi	London (Trainee representative)
Sue Watkin	Chair, Huntington's Disease Association
William Whitehouse	Nottingham (Paediatric Neurology)
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