Co-ordinated Arrangements for Genetic testing for Rare Disorders

1. Preamble

This document has been drawn up by a joint working party of the Clinical Genetics Society and Clinical Molecular Genetics Society, the two constituent groups of the British Society for Human Genetics that are particularly concerned with the provision and performance of molecular testing for genetic disorders.

2. Introduction

Diseases where there is a requirement for NHS molecular genetic testing fall into three categories:

2.1 A limited number of relatively frequent single-gene disorders, such as cystic fibrosis, Huntington disease and Fragile-X syndrome. These fit well into the existing organisation of regionally based molecular genetics laboratories.

2.2 A much larger number of individually rare diseases which collectively add up to a substantial part of the clinical workload of genetics services, but where demand within a single region is insufficient to justify setting up a laboratory service.

2.3 Common non-inherited diseases where genetic factors confer susceptibility. The degree of susceptibility that is genetically determined may not be critical to the health of an individual, but testing may permit definition of the pathophysiological sub-type and selection of more specific treatment or appropriate lifestyle changes. At present few relevant genetic factors have been identified, but this is likely to change.

2.4 This document concerns the second category of diseases. These can be defined as those where the current total UK genetic testing workload is stable and clinical demand is less than 100 requests per year. Examples of these so-called 'orphan' diseases include Tuberous Sclerosis and Von-Hippel Lindau disease (see appendix). This is a growing problem, given that many more diseases are becoming open to diagnostic testing with the rapid progress of the Human Genome Project and related work.

2.5 There is a substantial current unmet need in genetic testing for rare disorders. A particular problem is the frequent discontinuity between the ending of research funding in individual disease studies and establishment of a service. This problem has been recognised by the European Union Research and Technological Development Framework Programme V and more precisely by the House of Commons Science and Technology Committee in its report *Human Genetics: the Science and its Consequences* 1994/5 - paragraph 13 5. *'It is particularly distressing that diagnosis for a rare inherited condition can be offered on one occasion since it is part of a research project, and withheld on another.'*

2.6 Within the present system there are several obstacles to establishing services for rare diseases:

2.7 Purchasers see too little demand from their population to justify establishing a service for any one disease.

2.8 Inefficiencies and inconsistencies within the Extra Contractual Referral system as a mechanism for funding service for rare disorders.

2.9 The NHS internal market inhibits the co-operation between centres required to co-ordinate services for rare disorders and its abolition gives the opportunity to review and facilitate this.

3 Principles:

3.1 The ideal number of centres for *any one* rare disease is two. Having two centres provides the back-up necessary for reliability, facilitates quality assurance and encourages efficiency. Inefficiencies will develop and quality will suffer if services involving small numbers of cases are provided in a large number of centres.

3.2 Availability of diagnostic services for rare disorders should be comprehensive and not dependent on the area of residence of the patient/family concerned. A reliable mechanism is required to ensure local access to the *existing* network of national specialist services.

3.3 The UK should be largely self sufficient in clinical molecular genetics testing.

3.4 Any scheme should fit into current funding and contracting arrangements but also be compatible with changes to the funding of specialist and Supra-Regional Services as outlined in the April 1998 Consultation Document 'The New NHS - Commissioning Specialised Services.'

3.5 There is a need for a continuing overview of services and identification of developing need for genetic testing for rare disorders, with input from laboratory service providers, clinicians and patient groups.

3.6 Beginning the scheme does not necessarily involve 'new money' but it does require an audit of current R&D and ECR funding in this area (see appendix 2) and a co-ordinated response to the need for genetic testing for rare disorders. It requires a *new recognition* at all levels within the NHS that start-up funds are required to evaluate services for rare genetic disorders. In addition it requires that this type of work, although having a very short lag time from research to service and often existing in intimate contact with research is more properly thought of as service evaluation and not fundamental biomedical research.

3.7 The scheme is designed to foster a comprehensive coverage and to improve access to testing through widespread and efficient dissemination of information to clinicians and other health-care professionals on services for rare genetic conditions.

4 Proposal:

4.1. Identification of need. The proposed Joint Medical Genetics Committee of the Royal Colleges of Pathologists and Physicians and the BSHG (which envisages representation from other Royal Colleges and patient interests) could be a mechanism to consider unmet need in rare disorders and to issue recommendations on areas requiring service development.

4.2. UK Specialist Genetic Testing Network (UKGTN). The scheme should be organised as the UKGTN, with the aim of promoting efficient and comprehensive services of high quality for molecular diagnosis of rare genetic disorders. It should work through the existing clinical molecular genetics laboratories and consultant clinical geneticists.

4.3. Access. A Web site should be established (preferably via the UK HGMP Resource Centre) to provide a service list including UKGTN categories. An updated hard copy list should be provided on an annual basis.

4.4. Monitoring performance. Test turn-round times for current categories of disease and technique should be surveyed and target turn-round times published. In addition sample export and import between laboratories and new activities established under the UKGTN heading should be monitored. The CMGS Audit Committee is already active in this area.

4.5. Measuring and maintaining quality. Mechanisms to introduce External Quality Assessment for rare disorders should be considered through the UK Molecular Genetics Quality Assessment Steering Committee and the European Molecular Genetics Quality Network.

4.6. Funding requirement. Two centres should be considered for each disease and joint bids should be encouraged. Resources for each bid would need to be fully justified, but a centre might typically bid for one WTE scientist or technician, consumables and dedicated equipment.

4.7. Funding options. Possible mechanisms for funding the UKGTN include:

- Through an audit and stabilisation of *current* ECR activity in genetic testing for rare disorders (see appendix 2)
- through the NHS central R&D programme for an initial period of development and evaluation
- by top-slicing via supra-regional funding
- by regionally-based funding with addition of payments on a cost per case basis
- by central funding of start-up costs, then payment on a cost per case basis.

4.8. Invitation for bids to establish service. A mechanism should be devised to allow bids to be submitted and peer reviewed.

Members of the Working Party:

- **Professor Dian Donnai, President of the Clinical Genetics Society**
- **Mr Roger Mountford, Head of the Regional Molecular Genetics Laboratory, Liverpool Women's Hospital**
- **Professor Peter Harper, Chairman of the Royal College of Physicians Genetics Committee**
- **Dr Rob Elles, Secretary of the Clinical Molecular Genetics Society**

Appendix1* – estimated genetic testing workloads in some common and rare inherited diseases – some diseases which might come under the **UKGTN** heading are highlighted

Numbers of patients with common and other selected genetic diseases* and their relatives, who may require advice and testing through a clinical genetics service. (The numbers are based on a typical health authority district with 3,000 births annually and a total population of 250,000).

Condition	Birth frequency[1]	New cases per year in district	Approximate number of living patients in district	Approximate number of unrelated families	Approximate number of relatives at risk > 1 in 10 of being affected or of being carriers
Autosomal dominant disorders					
Huntington's chorea	1/3,000	1.0	18	14	162
Familial polyposis coli	1/8,000	0.4	8	6	50
Adult polycystic disease of kidneys	1/1.000	3.0	55	43	330
Familial hypercholesterolemia	1/500	6.0	394	355	2360
Tuberous sclerosis	1/12,000	0.25	19	12	70
Neurofibromatosis	1/2,500	1.2	69	30	280
Von-Hippel Lindau disease	1/100,000	0.03	1.3	0.8	10
Retinitis pigmentosa	1/5,000	1.6	36	32	220
Bilateral retinoblastoma	1/30,000	0.1	8	5	230
Myotonic dystrophy	1/7,000				
Autosomal recessive disorders					
Cystic fibrosis	1/2,000	1.5	25	20	50
Adrenal hyperplasia	1/10,000	0.3	23	20	46
Friedreich's ataxia	1/54,000	0.06	2	1.7	4
Spinal muscular atrophy	1/10,000	0.3	3	2	46
Phenylketonuria	1/13,000	0.2	18	15	36
Usher's syndrome	1/27,000	0.1	9	6	18
Sickle cell disease in Afro-Caribbeans	1/250	Estimate: actual figures depend on ethnic characteristics of the population and uptake of screening and offer of prenatal diagnosis			
Thalassaemia					
in Cypriots	1/140				
in Indians	1/1,000				
in Pakistanis	1/300				
X-linked recessive disease					
Duchenne/Becker muscular dystrophy	1/9,000	0.3	8	7	78
Haemophilia A and B	1/20,000	0.15	11	7	66
X-linked retinitis pigmentosa	1/7,000	0.43	23	14	70
Other X-linked eye disorders	1/7,000	0.43	23	14	70
Fragile-X syndrome	1/4,000	0.75	52	49	360
Other forms of X-L mental disorders	1/4,000	0.75	52	49	360

Chromosomal disorders					
Unbalanced translocations	1/2,000	1.5	16	16	60
TOTAL	1/144	20.8	987	730	5056

*Non-recurrent genetic diseases such as Down syndrome are not included.

**These figures describe only severely retarded children.

Notes

1. Birth frequency: many of these birth frequencies are changing, and those listed here refer to the most recent figures. For example, the birth frequency of Duchenne muscular dystrophy has fallen from 1 in 6,000 to 1 in 9,000 as a result of genetic counselling. The birth frequency of thalassaemia in Cypriots has fallen to 0, as a result of antenatal screening, prenatal diagnosis and the offer of selective termination of pregnancy.

2. Prevalence of living patients: This figure is based on the birth frequency, and the average duration of disease, compared to that in the general population. This too is changing, as treatments become more successful.

3. Number of unrelated families. These numbers are based on experience obtained from family studies. For example, for various dominant diseases, there are 0.42-0.9 families per living index patient, for autosomal recessive diseases the figures range from 0.64-0.85, and for X-linked diseases the figures vary between 0.63 and 0.87. The variation depends upon the proportion of cases that are new mutations, and the proportion of affected members of families who are living at any one time.

4. Numbers of relatives at risk: These numbers are also based on experience. On average, there are:

a) 3 high risk relatives for each patient with an X-linked disorder in which mutations are common (such as Duchenne muscular dystrophy);

b) 6 high risk relatives for each patient with an X-linked disorder in which mutations are rare (such as Fragile-X syndrome);

c) 6-9 high risk relatives for each patient with an inherited autosomal dominant disorder (such as Huntington's disease);

d) 2 high risk relatives for each patient with a dominant disorder;

e) 2 high risk relatives for each patient with an autosomal recessive disorder;

f) 4 high risk relatives for each patient with a chromosomal translocation.

For diseases of short duration relatives of dead patients are also counted. These numbers will fall once genetics departments have ascertained all families and there will then be a workload related to the number of new non familial cases born each year, together with the work necessary to keep families fully informed and tested with up-to-date techniques.

With further ascertainment it may be found that in some instances the figures given are under estimates. For example 5400 patients with haemophilia A and 1092 with haemophilia B were known to UK Haemophilia Centres in 1991.

Data taken from: Royal College of Physicians of London. Purchasers' guidelines to genetic services in the NHS. An aid to assessing the genetic services required by the resident population of an average health district. London Royal College of Physicians 1991.

* The appendix is modified from 'Population Needs and Genetic Services – An Outline Guide', 1993, HMSO Dd DH004322

Appendix 2

Calculated costs of molecular genetic testing currently funded by ECR's in the UK*

Audit year	ECR referrals	Total number of samples processed	Total number of genotype tests	Genotype tests/ sample	Estimated ECR value @ £50/genotype	% change in ECR activity (1994-5 =100%)
1994 -5	3029	52,694	144,568	2.74	**£415,000**	0
1995-6	4193	57,380	142,023	2.47	**£518,000**	+38%
1996-7	4766	61,817	159,527	2.58	**£615,000**	+57%

*** data from Clinical Molecular Genetics Society audit**