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Genetics and mainstream medicine

Service development and integration

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Key policy points

The development of genetics in mainstream medicine was one of the key themes of the 2003 Genetics White Paper, *Our Inheritance, Our Future*. Experience during the last seven years, together with the exponential development of technologies as set out in the House of Lords *Genomic Medicine* Report provide increasing evidence of the challenges of integrating genomic knowledge into clinical medicine. In this paper we provide analysis and recommendations for a strategic response relevant mainly to the management of inherited or heritable disorders.

Based on detailed strategic needs assessments in ophthalmology and cardiovascular disease and in consultation with interested organisations, genetic services and individuals we suggest a strategy to strengthen and integrate genetics in relevant clinical specialties. Central to this is the concept that, rather than specialist genetics 'moving into mainstream medicine', the clinical specialties should develop and expand to bring a set of new genomic technologies within their specialist remit. This will involve sub-specialisation in inherited conditions within the specialty and development of pathways for appropriate referral from more generalist 'mainstream' services as well as appropriate support from specialist genetics. Though the axis of clinical responsibility may shift, regional genetics services are and will remain an essential element of this paradigm. It will thus be vital to maintain the high quality, capacity and integrity of regional genetics services.

The current pattern of 'joint clinics' in which specialties work side by side with genetic services to provide care for patients with inherited disorders is highly regarded by patients and families. However, provision of such services is not realised equitably across the UK even now and will become increasingly difficult with further expansion of genetics in other clinical services. Further, our detailed policy work with a wide range of stakeholders in these fields leads us to suggest that it is time for the specialties (and those responsible for commissioning them) to include inherited disease within their own remit and appropriately integrate the necessary specialist clinical and laboratory genetic expertise.

A strategic response is required to move towards this integrated, specialty led pattern of care. Underpinning this response is the vital role of specialist clinical and laboratory genetics to continue to provide the necessary tertiary and quaternary services, support those providing care for people with heritable disorders in other specialties and help to lead policy development. The strategy will need to be developmental and will take place over a number of years, requiring continuing investment and commitment to service reconfiguration.

Evidence of increasing need for genetic aspects of mainstream medicine includes the following:

1. High numbers of patients and families due to greater knowledge of the prevalence of the conditions
2. Further patients identified from population screening programmes and systematic cascade testing
3. New diagnostic methods and treatment options, which can make a significant difference to outcome by enhanced and targeted health surveillance
4. Recognition of complexity of inherited conditions which requires input from both mainstream specialist and geneticists
5. Increasing capability for diagnostic testing with development for higher throughput of testing
6. Wider utility of genetic testing to include reduction in morbidity and mortality, information provision, assisting with reproductive decision making and improving care pathway.

We recommend the following prime elements for the strategic response:

Comprehensive engagement of specialised commissioners and provision of support to all commissioners in clinical areas where there are substantial elements of inherited disease. Such support should include, on a national basis, the development of commissioning guidance and agreeing clinical pathways involving primary, secondary and specialist elements of care.

A programme to reduce the current inequities that exist across the UK in access to high quality services for inherited disease within the various clinical specialties. The response will require increased overall capacity and some service reorganisation to ensure critical mass.

The development and strengthening of mechanisms such as clinical networks to support specialised inherited conditions services and to ensure rapid translation of advances and most efficient use of available expertise and experience.

There should be a review of genetic test provision to respond effectively and efficiently to increasing demand, rapidly developing capabilities and changing technologies. This should be undertaken in the context of national pathology modernisation and should include how laboratories can best respond to increased demand for testing, how to maintain quality in NHS services, appropriate gate-keeping and the development of mechanisms for requesting, funding and providing genetic tests and how genetic tests should be evaluated and regulated.

An increase in the sub-specialist workforce able to provide the specialised elements of services for inherited diseases. This must be accompanied by continuing work to develop competencies in genetics in the health professional workforce with development of strategies aimed at medical, nursing, and other supporting professions.

Development and evaluation of methods for family record keeping and cascade testing for

clinical specialties other than genetics. Research and development must be coordinated across specialties to prevent duplication and potential incompatibility of systems. Unresolved questions about the sharing of data across kindreds, particularly in relation to the introduction of electronic patient records, must be addressed by policymakers through work with relevant clinicians, patient groups, and legal and IT experts.

Development and evaluation of models to ensure effective and efficient provision of specialist genetic support to other clinical services.

Implementation of audit and research programmes to evaluate effectiveness and cost-effectiveness of inherited disease services. This is vital in a climate where health services will need to be prioritised and recognises the current paucity of evidence about the overall effectiveness of specialised services and genetic testing in improving outcome for patients and family members.

The House of Lords, in their report on *Genomic Medicine*, commented that '*The White Paper could hardly have anticipated the remarkable advances since 2003'*. The complexity of the relation between genotype and phenotype, together with expanding capacity to fine-tune diagnosis and management based on an understanding of both requires an expert service response. This, together with the anticipated scale of service need across many specialties and including clinical and laboratory elements, will provide a challenge that, we believe, can only be met by remodelling of the relationship between specialist genetics and other clinical specialties. This must be supported by strong and expert commissioning covering whole care pathways, effective and efficient laboratory services and major workforce development. Without such a fundamental strategic approach, agreed and supported by all major stakeholders, there is a danger that the health benefits from scientific innovation in genomics will not be realised with equity across the UK.

We recommend this report to those charged with developing strategies for genomic medicine for UK health services, and particularly to the Human Genomics Strategy Group.

1 Introduction

The greater inclusion of generalists in giving genetic care to patients was first signalled in April 2001 by the Secretary of State for Health who noted that the NHS needed to 'change and adapt its services' to meet the challenge of genomics[1]. Genetic services would need to spread from specialist centres and into GP surgeries, health centres and local hospitals. In other words, genetic services would become more 'mainstream'. In 2003 developing genetics in mainstream services was one of the main themes of the Genetics White Paper[2] with substantial initiatives in modernising laboratories to provide essential infrastructure, engaging other specialties to 'spur the take-up of genetics' through service development pilots in the hospital sector and developing GPs with a Special Interest in Genetics. It was expected that specialist genetics centres would play a leading role in *'spearheading diffusing genetics knowledge and expertise across the NHS'*[2].

Between 2006 and 2009 PHG Foundation undertook a detailed consideration of the diffusion of genetics and development of services for inherited disorders in two clinical areas [3,4]. The findings and recommendations in these reports were then considered in the light of the expectation that there will be similar needs and issues across a range of other clinical services. Requirements in relation to single gene disorders may be further augmented by the future integration of genetic aspects into the management of common complex disease. The widespread use of genetic technologies in other areas of clinical medicine, such as the characterisation of tumours to fine-tune cancer treatments, and the exponential rise in use of new sequencing technologies, as set out in the House of Lords *Genomic Medicine* Report[5], will add yet another dimension and further increase the imperative to service development.

Overall, our analysis challenges the idea of 'genetic services' becoming 'more mainstream' but emphasises the continuing highly specialised nature of care for patients and families with inherited disease. However we do propose a shift of the axis of main clinical responsibility for individual patients with inherited disease from clinical genetics to the relevant specialty-cardiology, ophthalmology, renal medicine, neurology or a host of other areas. Thus we propose a future in which, rather than genetics 'moving into mainstream medicine', other clinical areas develop and expand to integrate new clinical expertise relevant to inherited disease and a new set of genomic technologies into clinical pathways as relatively specialised areas within their own service and with appropriate support from regional clinical genetics centres. In advocating this paradigm we emphasise the need for leadership and close co-operation with the specialist clinical and laboratory genetics service to promote and sustain such development.

We advise that configuring and developing a range of clinical services in this way - with close relationships with regional genetics services - would provide a solid foundation for the later integration of wider genomic technologies, such as those now being developed for stratified medicine in a range of conditions, into clinical practice.

2 Background

In the 1998 Royal College of Physicians document *Commissioning Clinical Genetic Services*[6] specialist genetics services were acknowledged as providing for: the diagnosis of inherited disorders including congenital malformation syndromes; genetic counselling and associated support; up to date information on the availability of genetic testing; and support and management, especially in the light of genetic test results. There was close liaison between clinical geneticists and laboratory genetic services to allow clarification of clinical factors and interpretation of genetic risks and to ensure the appropriateness of investigations.

At this stage, therefore, much of the emphasis was on diagnosis of rare genetic conditions and syndromes. Geneticists are expert at recognising these syndromes, often on the basis of particular combinations of clinical signs and symptoms and recognition of family history patterns. As now, they advised on risk of recurrence, discussed reproductive options for parents and other family members, and provided information for testing for patients and others who might also be at risk either directly or by passing on the genetic abnormality.

As they were often dealing with severe, highly penetrant disorders for which prevention options were limited, there was much emphasis on genetic counselling before and after genetic testing and acute awareness of the need to ensure that *'wider family and social and ethical factors are fully considered'*. Huntington's disease provides an example of the need for counselling where the condition is almost 100% penetrant, almost invariably severe and there is currently no preventative treatment.

An important point, relevant to subsequent consideration of overall clinical responsibility for patients with inherited disease, is that most geneticists have not usually been expected to provide clinical care and treatment for the phenotypic manifestations of disease, although in the absence of overall care managers they have often adopted a leadership and coordinating role for some multi-system disorders liaising closely with other involved specialties.

The completion of the Human Genome Project in 2003 set the stage for an era in which inherited disorders would be characterised at a molecular level in almost every area of clinical medicine. It was said that 'genetic services will spread out of specialist centres into GP surgeries, health centres and local hospital'. Bringing this about was thought largely to be a matter of education of health professionals, further development of clinical and laboratory genetic services and the development of clinical services through demonstration pilot studies. These initiatives were supported by NHS Genetics White Paper monies. The formal evaluation of the service development pilots provided evidence mainly about the organisational issues that arise as new genetic services are introduced into mainstream specialties[7]. More clinical experience has been gained in these and other centres where inherited disease services have been provided in a variety of ways, such as through joint genetic/clinical specialty clinics. Between 2006 and 2009, the PHG Foundation worked with multidisciplinary Working Groups' to examine inherited disease services in two clinical areas: cardiology and ophthalmology; to assess health needs for genetics elements of services; to consider the necessary response to those needs and review the availability of current services.

In the current paper we generalise from these detailed individual reviews to consider the implications for the provision of services if, as is expected, the needs are as great in a range of other specialties and the science and available technologies continue to develop apace. This paper is in two main sections. Firstly, we describe key factors that have influenced emerging health 'needs' for genetics in mainstream medicine. Secondly, we make proposals for policy responses, based on recommendations developed through our two expert Working Groups and wider consultation in other clinical and laboratory specialties.

3 Methods

Programmes of needs assessment were undertaken with leadership from the PHG Foundation in two areas of clinical medicine - ophthalmology (2006 to 2007) and cardiovascular disease (2007 to 2009)[2,3]. The Working Groups involved multidisciplinary membership including consultants with relevant clinical focuses, other professionals from the relevant specialty, clinical geneticists, genetic counsellors, laboratory scientists, general practitioners, commissioners, representatives of patient organisations. The full membership is given in the relevant reports. Each Working Group met four times and between meetings supportive background work was undertaken by PHG Foundation team members, (where necessary with further co-opted individuals). This work included epidemiology, background literature reviews of service evaluations, development of case histories to describe specialised aspects of the services, survey of current services, consideration of ethical, legal and social aspects and wider focus groups with patients. Following assembly of the above information, the groups devised their own set of recommendations for their final report. Examples from the detailed needs assessments are used to illuminate particular issues in this paper.

Both final reports and recommendations were then considered in the light of expected similar developments in other services. This resulted in a draft paper *Genetics and mainstream medicine - achieving the transformation*, which was sent out by UKGTN in February 2009 to professional groups associated with a wide range of other clinical services, such as the Association of British Neurologists, and through consultation channels to professional groups within the BSHG. Comments were received from 23 individuals and groups, summarised and incorporated as appropriate into this current paper. A copy of the summary of consultation can be found on PHG Foundation website: www.phgfoundation.org.

4 Emerging health needs for genetics in mainstream medicine

Health 'needs' for genetic services are a function of two main elements: **epidemiology** - the breadth, prevalence and health impact of relevant conditions; and **effectiveness** – the capacity to benefit, which comes from enhanced ability to diagnose, prevent or treat conditions. During recent years advancing knowledge in all of these areas has meant that health 'needs' have increased and widened, with increasing 'need' arising for specialised inherited diseases within many clinical specialties. This increasing 'need' is discussed in the following main areas:

1. Need to focus on inherited or heritable conditions
2. Increasing recognition and characterisation of inherited conditions throughout clinical medicine leading to high total population prevalence
3. Screening programmes, family tracing programmes and better clinical practice regarding risk to family members leading to identification of more patients
4. Complexity of genotype-phenotype relationship meaning that clinical assessment and genetic test interpretation require a true partnership of clinical and genetic expertise
5. Increased capability for genetic testing
6. Wider utility of appropriate genetic testing with some shift of focus to include diagnosis, disease prevention and management

4.1 A focus on inherited or heritable conditions

The use of the word 'genetic' needs clarification. The present discussion is centred on how inherited or heritable diseases are identified, diagnosed and managed. Testing of DNA may, or may not, be part of this management programme. Many of the ophthalmological conditions (for example X-linked retinoschisis, characterised by splitting of the retina, which can cause loss of vision) can be diagnosed clinically on the basis of characteristic appearance of the fundus, electrophysiological testing of the retina and family history. The fact that diagnosis of such disorders has implications for family members provides a common thread. Knowledge of possible inheritance patterns imposes a responsibility to consider risk, and prevention options for other family members.

In contrast, technologies based on a knowledge of DNA and its products are widely used within health services, such as, for example, the use of gene expression profiling to determine treatments in chronic myeloid leukaemia (using the targeted drug therapy *Imatinib)* or to decide on the use of the drug Herceptin® (*Trastuzumab*) in breast cancer. The development and application of such tests has taken place within the context of clinical cancer and other services and their associated laboratories and does not require expert clinical or laboratory genetic interpretation. Such genomic medicine is therefore not considered further in this discussion.

4.2 Wide range and total prevalence of genetic conditions throughout clinical medicine

The large number and wide range of inherited conditions recognised throughout clinical medicine provide a challenge to health services and to specialist genetics services as they

are currently configured. The present discussion is limited mainly to consideration of single gene or chromosomal disorders (the main inherited or heritable conditions). However, increasing knowledge about the contribution of genetic factors to complex chronic disorders such as heart disease, cancer or psychiatric disease emphasises even further the need for all specialties to incorporate genetic consideration into their diagnostic, preventive and treatment models.

More than 50 inherited cardiovascular conditions are now recognised including the broad categories of inherited arrhythmias, cardiomyopathies, arteriopathies, and numerous syndromic conditions. Overall in the UK such conditions are thought to affect over 200,000 people[4]. A further 120,000 individuals are estimated to be affected by familial hypercholesterolaemia, which causes premature disease of the coronary arteries[4].

Public health work on epidemiology of blindness and partial sight in the UK provides evidence that inherited eye disorders account for approximately one third of the 450 children diagnosed as blind or severely visually impaired each year, and about 10% (250) of the 2,500 adults of working age who receive blind certification each year[8,9]. As well as some more common conditions, such as retinitis pigmentosa, which has a birth prevalence of 1 in 3-4,000, we identified 74 groups of monogenic conditions that primarily affect the eye. In total, using best estimates from literature on birth prevalence we estimated that there would be around 1,500 new cases of monogenic eye disorder with significant eye manifestations each year in the UK[3].

Finally, widening the scope across clinical medicine, the molecular basis is now known for more than 2,700 disorders for which the phenotype is well described[10]. Physical manifestations are spread across disease involving every system of the body (and thus most clinical specialties). Whilst this figure does not imply that there are tests with clinical utility for 2,700 disorders (see later discussion), it does underline the emerging potential of genetics in most areas of medicine.

4.3 Increased diagnosis through screening, family tracing (cascade testing) and good clinical practice

With new screening programmes, formal cascade testing systems and more systematic and better developed clinical practice that properly identifies and follows up individuals at risk, the need and demand for services for suspected and diagnosed inherited conditions will rise rapidly.

New screening programmes such as those for sickle cell and thalassaemia, medium chain acyl CoA dehydrogenase deficiency (MCADD) and cystic fibrosis have already increased the numbers of new cases detected and demand for follow up testing and testing of family members. For MCADD the new screening programme pilot identified 87 cases in nearly 750,000 newborn babies screened - a rate of 1.2 per 100,000[11]. It is estimated that newborn screening programmes will identify 2-3 times more affected individuals than those who would present clinically[12].

The use of family tracing such as that proposed for familial hypercholesterolaemia (FH), whether as organised cascade screening programmes or as enhanced clinical management of cases, means that the overall numbers coming into contact with services will increase.

Sudden cardiac death provides a further example arising in cardiovascular services where, under the new National Service Framework, pathologists are recommended to take samples to determine a possible genetic basis for the death (for example the cardiac arrhythmia Long QT syndrome) with a view to identifying and advising at-risk relatives[13].

In all areas where we have conducted detailed needs assessment (including work in inherited metabolic disease[14]), clinical best practice involves the following up of potentially at-risk relatives. All of these individuals will need to be tested and/or clinically assessed within the mainstream specialty, meaning that the numbers of patients requiring referral will rise rapidly. Although we might envisage that eventually some sort of 'saturation' of the population might be reached, the fact noted in the inherited cardiovascular review that cascade testing currently rarely reveals individuals already known to the service suggests that we are a long way from reaching this point[4].

4.4 Complexity of clinical and laboratory assessment and management

The complexity of the relationship between genotype and phenotype and the use and interpretation of genetic testing must be recognised. This complexity, together with the rareness of individual conditions provides a challenge to the concept that care for people with inherited disease should become 'mainstream' in the sense that all services should provide it. Our evidence suggests that it should be developed as a specialised area of the relevant clinical specialty where experts from the host discipline and specialist genetics must work in partnership to bring together clinical and molecular assessments. This usually requires access to highly specialised investigations including genetic testing and a range of other examinations, together with the capability to provide expert interpretation. Examples from cardiovascular medicine are provided in Box 1.

Box 1. Specialised elements of inherited cardiovascular disease services

Cardiological investigation for inherited disorders may involve a range of examinations including detailed analysis of the ECG, assessment of symptoms by exercise testing, and echocardiography or cardiac magnetic resonance imaging to detect defects in heart structure and assess their effects on function. Substantial experience and expertise are required to distinguish ICCs from the more common forms of heart disease. Genetic testing, where available, can help to confirm or refine a provisional diagnosis. However genetic findings are not always clear-cut; for example, genetic testing may reveal sequence changes that are difficult to interpret and whose pathogenicity is uncertain. Both clinical and genetic findings must be considered in the light of other features of the patient such as age and sex, clinical history and family history. In some cases, clinical and/or genetic investigation of other family members may be necessary to help confirm or rule out a suspected diagnosis in the index case. This requires a multidisciplinary team approach with key input from a geneticist in the interpretation of such findings.

Understanding of the underlying molecular abnormality also shapes the advice and treatment offered to the patient. Box 2 provides an example of this for Long QT syndrome (LQTS).

Box 2. Molecular diagnosis influences treatment for inherited cardiovascular condition

Long QT syndrome is an inherited condition characterised by an abnormally prolonged QT interval on the ECG and a predisposition to develop life threatening ventricular arrhythmias. There are now known to be at least 12 genes involved and well over 400 mutations that cause abnormalities in the cardiac ion channel genes that underlie the coordinated cardiac muscle cell contractions. Importantly, though our knowledge of associated natural history of disease and evidence on best treatment options remains incomplete, some tailoring of preventive and treatment advice to the precise molecular diagnosis is currently recommended. For example, in the LQT1 subset of LQTS sudden cardiac death is triggered most frequently by exercise (particularly swimming or emotion) while lethal cardiac events in LQT2 occur more often when the patient is roused by a sudden noise during rest or sleep[15]. Similarly, patients with LQT1 respond well to beta-blockers whilst those with LQT3 do not.

These examples serve to illustrate that, although the geneticist may be involved in advising on the ordering and interpretation of genetic tests and how to deal with family members, overall patient care must be managed by the cardiologist.

4.5 Increase in capability for diagnostic testing to deal with increased volume and complexity

In the 'pre-genomic era', genetic testing technologies were largely limited to Sanger sequencing or polymerase chain reaction (PCR). Whilst both of these key technologies are highly accurate, they can be time consuming and are hard to scale-up to meet higher demands and increasing levels of complexity.

Since the beginning of the 'post-genomic era', there has been an explosion both in the development of new genetic testing technologies and the overall quantity of sequence data. Detailed knowledge of the genetic sequence together with the availability of relatively low cost high-throughput technologies means that clinical genetic testing is now possible for many genetic disorders. This trend is expected to continue with the further development of genetic sequencing technologies.

Box 3 gives examples from the needs assessment work of the use of such new technologies to increase the capability and capacity for genetic testing.

Box 3. New technologies for gene testing

In ophthalmology microarray testing is now available commercially with chips aimed at particular diseases including Leber Congenital Amaurosis and Usher syndrome. This is thought to provide a useful first pass screening method for disorders that are genetically heterogeneous.

In cardiology developments have also allowed significant expansion in the number of genetic tests offered in the clinic although they are still limited. In this clinical area, mutational hot spots rarely occur, meaning that full gene mutation screening is invariably required to identify mutations that are unique to families. This is laborious and expensive and, in moderately heterogeneous families, such as HCM, DCH and LQTS, where up to five genes are currently tested, represents the diagnostic limits of current technologies.

For FH a kit is now commercially available that tests for 20 of the most common FH-causing mutations in UK patients[16]. This has been reported to detect up to 50% of all the mutations detectable by a full gene screen, and can be completed within a week of sample receipt for a cost of approximately £50.

At a later stage, it is envisaged for both cardiology and ophthalmology that new technologies would enable identification of genetic variants affecting treatment response and susceptibility to underlying complex diseases. Careful assessment of these technologies will be required before access to such methods should be widely available. Not least will be the interpretive difficulties; for example there are likely to be multiple variants detected and identifying the causative variant(s), or establishing their likely significance may be difficult. This adds to the complexity of assessment, although it is expected that, as knowledge is gained and collated, for example through the mutation database complied at the National Genetics Reference Laboratory in Manchester[17] (UK Diagnostic Mutation Database (DMuDB)) some questions may gradually become more routine. www.ngrl.org.uk/Manchester/projects/informatics/dmudb

In the longer term cheaper, quicker and more powerful technologies, such as whole genome sequencing, as outlined in the House of Lords *Genomic Medicine* Report[5], could transform genetic testing services and may become more widely accessible within clinical specialties. Thought will need to be given to the context of their use and the competence of the professional ordering and interpreting them.

4.6 Wider utility of genetic testing

The decision to offer a genetic test within clinical practice should be based on a careful evaluation of the test, and on the individual circumstances of its clinical utility, or ability to assist the patient or family to an improved health outcome. As the paradigm of our understanding of genetic disease shifts, genetic tests have become more available and prevention and treatment options have increased. Genetic tests may therefore be offered to

a wider range of individuals, for a wider range of conditions for a wider range of purposes.

Many single gene disorders are very variable in their severity, age of onset, penetrance, and expressivity and in the degree to which they can be prevented and treated. Such differences have implications for the utility of testing and the conditions under which it should be offered.

The ultimate purposes of genetic testing are now agreed as follows[18]:

- To reduce morbidity or mortality
- To provide information salient to the care of the patient or family members and/or
- To assist the patient family members with reproductive decision making

Such outcomes may be achieved for the proband or family members in whom cascade testing becomes possible when the underlying molecular pathology is identified. They may also be achieved by providing information to assist and streamline the process of care. The peer-reviewed literature contains very few examples of formal evaluations of the clinical utility of genetic tests although there are an increasing number carried out through the "Gene Dossier" process for the UKGTN (see p23 section 5.4.3).

In our needs assessment we therefore used ophthalmology to explore some case histories through which clinical utility in these dimensions can be demonstrated.

Genetic testing might, for example, now be the simplest and cheapest way to make a diagnosis in the first instance and thus provide aetiological and prognostic information or inform management or treatment decisions for patient and family.

> In **X-linked retinoschisis** the presentation can be atypical. A genetic test of the one gene *RS1* associated with the condition in nearly 90% of males with the condition could be the quickest and easiest way of making the diagnosis.

Genetic testing can be used to make an earlier, more complete diagnosis in order to give more precise information about prognosis and provide the best supportive care.

> The provision of a genetic test for **Usher syndrome** in the child with congenital hearing loss can confirm that the child has the condition and will go on to develop the characteristic retinitis pigmentosa and progressive visual loss. Such information allows parents to be advised on early cochlear implantation for their child to ensure maximum development of communication.

Genetic testing can lead to improvements in the process of care that can have a direct effect on the patient and at-risk relatives.

In **retinoblastoma**, genetic testing is an important part of clinical management. It is used to test whether the condition is caused by a germline or somatic mutation. For the patient a germline mutation would have consequences for surveillance, implying the need for careful surveillance of the symptomatic eye (if not enucleated) and also the contralateral eye. Determination of a germline mutation also allows relatives to be tested and surveillance (requiring examination under anaesthetic) offered only to those who test positive. It also gives parents the option of prenatal testing for future pregnancies.

This widening of circumstances in which genetic tests might be offered has implications for the clinical and laboratory support provided to support decision-making for patients within the care pathway. For example, in circumstances where the clinical utility of genetic testing is clear-cut, such as when a preventable or treatable disease can be diagnosed, it is now accepted that there is not necessarily the need for in-depth genetic counselling such as may be provided by a genetic counsellor. In some clinical areas, such as cancer genetics, the necessary level of counselling may be provided by cancer nurses who have had special training in the genetics of the disease and the impact on the wider family. These nurses must retain close links with cancer geneticists in local regional genetics centres who provide professional oversight.

Nonetheless, in many circumstances where testing is proposed, patients, parents and other relatives will require help to understand the complexities of testing (for example, factors such as mosaicism or incomplete penetrance) and will require skilled support to understand the possible implications for themselves. The competences required in the health professional providing such support must be adequate but need not necessarily be provided by a clinical geneticist or counsellor. Tests could increasingly be undertaken by clinicians who have a special interest in inherited conditions within their own specialty and who have developed the necessary competences.

4.7 Implications of evolving health needs

In summary, the large numbers of patients affected, the multiplicity of genes known to be involved in inherited disease, the complexity of emerging understanding of genotype-phenotype associations within any one specialty, and our expanding capability to improve diagnosis and management on the basis of genetic understanding amount to evolving health needs that provide a set of challenges to current health services:

- There will not be enough capacity for specialist geneticists (whether consultant or genetic counsellor) to provide genetic elements of clinical care for all patients in all clinical areas

- Patients and at-risk relatives will need to be diagnosed in specialised services having a partnership between the relevant specialists and geneticists

- The complexity of assessment means that it is not suitable to be undertaken in general service clinics (eg cardiology and ophthalmology). Follow-up care may sometimes be devolved to the general clinics.

- Although specialists in genetics need to have an input to the specialised inherited disease service each patient may not need to be seen or assessed by a clinical geneticist or genetic counsellor before genetic testing is offered

- As knowledge develops on relationships between abnormal variants and different phenotypes, the provision of formal evaluative and interpretive support alongside tests may allow tests to be used by a wider range of physicians for their patients.

5 Policy response to expanding genetic 'need'

The speed of advancing science and clinical applications, and the rapid expansion and complexity of 'need' outlined above in the two specialties examined, has impressed on us the requirement for an urgent and fundamental policy response that will be relevant to many other specialties. The response must be based on an articulation of the overall population health 'need' for genetic aspects of clinical and laboratory services. It must ensure the development of specialised 'inherited disease' services within clinical specialties, the use of genetic tests at appropriate points by health professionals with the necessary expertise and the clinical integration of genetics within care pathways leading to and from primary care and district hospital services. It must also recognise the realities of the current limited services in the UK to diagnose and manage patients with inherited conditions.

Underpinning all of this response will be the vital role of specialist clinical and laboratory genetics to provide the necessary tertiary and quaternary services, to continue to develop and maintain the highest technical and ethical standards of care, to support those providing care for people with heritable disorders in other specialties and help to lead policy development.

The policy response should include the following areas:

1. Engagement and development of capability and capacity of specialised commissioners and commissioners of clinical services where there are substantial elements of inherited disease
2. A programme to develop high quality, specialised and equitable services for inherited conditions
3. Mechanisms (such as clinical networks) to support developing services
4. Review of genetic test commissioning, funding, provision, evaluation and regulation
5. Increasing skills and developing capacity in inherited disease relevant to specialised and more general health professionals
6. Developing and evaluating methods for family record keeping and cascade testing that can be used within or accessed from mainstream medicine
7. Development and evaluation of models for integration of genetics in other clinical specialties
8. Building audit and research programmes to evaluate effectiveness and cost-effectiveness of services of inherited disease services

In the following paragraphs we provide further analysis of these areas and make broad recommendations.

5.1 Development of commissioning capability and capacity

Recommendation 1

There should be wide engagement of commissioners of specialised services and of services in all clinical areas where there are substantial elements of inherited disease. The proposed National Commissioning Board should take a lead in the development of commissioning guidance for specialised services and for the integration of the necessary clinical pathways between primary, secondary and specialist elements of care.

Rare inherited conditions are found in many branches of medicine. Patients with clinical symptoms largely present to a particular specialty, where they require diagnosis and subsequent management. Genetic considerations can, and now should, add value to that interaction by ensuring that inherited disorders are recognised, the diagnosis (and hence the management) is as accurate as possible, with fine-tuning to molecular sub-divisions, and at-risk family members are identified and advised. The genetic input will have key clinical (family history taking, examination, interpretation and counselling) elements as well as laboratory elements. Assessing and managing patients with suspected or actual inherited diseases is likely to be a relatively specialised clinical area within any specialty.

We suggest that, in the services examined, commissioning for inherited disease within a specialty should be led by that specialty. This element of service should now be formally included in commissioning documents, contracts, service specifications and standards and should include explicit arrangements for clinical and laboratory genetics elements to be provided as part of a multidisciplinary team.

Formalised commissioning of inherited disease services for clinical management has largely not been undertaken so far. In inherited cardiovascular conditions, for example, only two of the nineteen services were expressly commissioned as part of the cardiac network provision.

Inherited conditions are likely to form an important subset of disease, but one that crosses many boundaries within the specialty (see Box 4). Within each specialty, therefore, the services need to be planned and commissioned, and clinical pathways built, to ensure that those with inherited conditions are identified within the district general secondary care services and primary care and referred for specialist advice. Once provided, shared care may be possible for long-term management of patient and family.

Box 4. Range of inherited conditions across ophthalmology and cardiovascular disease

In ophthalmology, inherited conditions might affect the retina, lens, cornea, optic nerve or any structures of the eye and so need to be considered within many subspecialist areas.

In cardiovascular medicine we have also noted that inherited conditions might come to the attention of those managing arrhythmias, cardiomyopathies, arteriopathies, hyperlipidaemias and coronary heart disease.

Developing high quality commissioning will be more straightforward for the small number of services that are included in the national definitions sets (the only area of inherited disease included is that of inherited cardiovascular disease[19] or where there is guidance from NICE (*e.g.* for familial hypercholesterolaemia)[20]. Because of the limited commissioning and public health expertise in genetic and genomic aspects of health care available across the UK, it will be important that the proposed National Commissioning Board takes a leadership role in preparing guidance on genetics across the range of clinical medicine in order to support local GP consortia commissioning.

Commissioning frameworks should be developed that cover the likely scope, size and nature of the clinical and genetic elements in the service and expected quality standards. Such guidance, prepared on a national basis, should include an indicative number of services that would be needed to ensure that each has critical mass for high quality, and should explicitly state that all centres would not expect to have their own service but should co-operate with neighbouring services to ensure access on a population basis. Examples of such commissioning frameworks developed as part of the PHG Foundation projects in ophthalmology and cardiology are available on the PHG Foundation website (www.phgfoundation.org).

As a complement to the mainstream specialty commissioning documents, the clinical and laboratory genetic input that would be required to support other specialties should be specified in guidance on the roles of clinical genetics services. This is also included as one of the national genetics specialised services definitions set (definition no 20)[21] in the UK.

It will be very important that clarification is achieved for commissioning purposes whether the genetic testing itself (as opposed to appropriate supporting referral and interpretive advice) is included within the genetic service or the mainstream service contract.

5.2 Development of high quality, specialised and equitable services for inherited conditions

Recommendation 2

High quality specialised services should be developed on an equitable basis across the UK. This will require increased overall capacity and some service reorganisation to ensure critical mass.

Our Working Groups considering clinical services focussing on inherited disease came to the conclusions that these were highly specialised areas of care requiring integration of clinical specialty and genetics elements.

In each specialty this is likely to require input from clinicians who have taken a special interest and developed experience in the relevant group of rare disorders. In particular they will need to be able to make expert assessments of the phenotype and have an understanding of the use and interpretation of genetic tests. Clinicians will need to have access to other supporting investigations (such as specialist ECGs or complex electrophysiological retinal tests). Genetics elements for all patients will include tasks such as family history taking and follow-up. Some patients may require specialist genetics expertise (eg identification of syndromes, reproductive counselling, interpretation of uncertain test results and complex ethical or legal issues).

Broad outlines in the definitions sets will need to be supported by commissioning frameworks that cover the likely scope, size and nature of the clinical and genetic elements in the service and expected quality standards. Such guidance, prepared on a national basis, should include an indicative number of services that would be needed to ensure that each has critical mass for high quality, and should explicitly state that all centres would not expect to have their own service but should co-operate with neighbouring services to ensure access on a population basis. Examples of such commissioning frameworks developed as part of the PHG Foundation projects in ophthalmology and cardiology are available on the PHG Foundation website.

In the UK such specialised services have largely been developed in centres where there are research interests and enthusiasms. However, our reviews revealed a plethora of small services, with very few providing comprehensive care and great disparities in quantity and quality of services between geographic areas. Box 5 provides further details.

Box 5 Examples of comparative service provision from the needs assessment work

In cardiovascular disease[22], we identified 19 providers of services for ICC, but of these five were based in London. Fifty nine percent of outpatient clinics and 60% of consultant staff time was in London. Eight of these services saw fewer than 200 new patients per year (four new patients per week). Across the rest of the UK there was a 10-30 fold variation between the highest and lowest level of provision on various measures of activity including numbers of new patients seen and genetic tests ordered. Using rates of new patient referrals for the London strategic health authority populations as a benchmark, we estimated that there was an unmet need of some 7,000 new referrals over the whole of the UK and that activity needed to be increased 3-4 fold for regions outside London to reach equity with the London provision.

For FH, there are approximately 130 lipid clinics throughout the UK, and in a 2008 HEARTUK survey six services were identified as managing more than 200 FH patients per year but 25 saw fewer than 25 patients. Again, services were concentrated in London and other metropolitan areas. Services for children with FH were particularly lacking, with fewer than 600 of the predicted 14,000 under 10 year olds currently having been identified and being managed in specialist clinics[23].

Similar findings from our work in ophthalmology[24] showed that there were 19 service providers, including two in London. A similar pattern was evident with a large number of small services, and only three services seeing more than 300 patients per year. Our needs assessment showed an estimated unmet need of 1,000 new patient referrals per year across the UK. Disparities in provision between SHAs in relation to population size showed a seven-fold variation in clinic sessions provided and new patients seen between the most and least active region.

The need for highly specialised clinical and laboratory services, coupled with the need to have sufficient throughput to justify critical mass of clinical and investigative resources necessary to make the service cost effective, leads to the inevitable conclusion that fewer services, each with greater patient throughput, will be required. This will require considerable political will and determination to implement.

5.3 Development of mechanisms (such as clinical networks) to support developing services

Recommendation 3

The development of mechanisms (such as clinical networks) to support specialised inherited conditions services and ensure rapid translation of advances and most efficient use of available expertise and experience.

In relatively small specialised services, such as those examined and services that are developing rapidly, it is important to use available expertise and experience efficiently; to have mechanisms through which good practice and ideas can be quickly shared and services can work collaboratively to develop resources such as guidelines and protocols, patient information or educational material. Facilitating such collaboration through a network of providers has been recommended as a result of all services examined in detail. Such networks would also be powerful fora to provide advocacy and leadership for the service on a national and international basis and for development of audit and research. For maximum effectiveness networks would require resources for leadership, programme development, coordination, and dissemination. Models for such networks exist in cancer genetics and non-genetic areas such as clinical haematology. Partly as a result of the Working Group on inherited cardiovascular conditions an association, the Association for Inherited Cardiac Conditions (AICC) now exists for professionals with an interest in this area www.improvement.nhs.uk/aicc/index.aspx (checked 07-10-2010).

5.4 Review of genetic test provision

Recommendation 4

There should be a review of genetic test provision to respond effectively and efficiently to increasing demand, rapidly developing capabilities and changing technologies. This should be undertaken in the context of national pathology modernisation and should include how laboratories can best respond to increased demand for testing, how to maintain quality in NHS services, appropriate gate-keeping and the development of mechanisms for requesting, funding and providing genetic tests and how genetic tests should be evaluated and regulated.

Our reviews of the two clinical areas exposed many issues around the provision of molecular genetic tests both now and into the future. Development of laboratory services are the subject of major national strategic work in the contexts of genetics services (Human Genomics Strategy Group) and national pathology services *Modernising Pathology Services*[25]. We set out here the main points arising in our reviews.

5.4.1 Capacity and quality of testing

Our cardiovascular disease review[4] showed a 20-fold variation in genetic test provision, in relation to population size (based on strategic health authority populations). Although there is no agreed 'right' level of provision, the rapid increase in patient referrals and testing that was reported as services became established would indicate that services with lower levels limited more by lack of capacity (or lack of recognition by referring physicians) than lack of need. It is suggested, therefore, that demand for testing will eventually level up towards the higher end of the distribution.

There has been a huge investment in the quality and capacity of laboratory services during the last 20 years, including the technology itself and the development of a network of genetic laboratories and scientists with unique expertise and knowledge about the interpretation of genetic analyses. However, there is now a danger that, as demand rises, other laboratories

start to undertake DNA and RNA based diagnostics without the required qualifications, training and background and unable to take advantage of the high throughput technologies that are available in the genetics laboratories.

As part of our review of inherited disease services in cardiology and ophthalmology it was recommended that economies of scale, quicker reporting times and the concentration of interpretive expertise in support of particular clinical areas could be achieved by focusing activity in two or three molecular genetics laboratories. These laboratories would provide a comprehensive testing service which, subject to UKGTN assessment, may be approved as a national service and listed on an online database.

Finally, the developing capacity for molecular genetic testing must be underpinned by parallel developments in bioinformatics that will support clinical decision-analysis. This is a critical national strategic issue that was outlined in the House of Lords report on *Genomic medicine* and will be critical to the successful development of clinical services for heritable, and a wide range of other, disorders.

5.4.2 Developing appropriate mechanisms for requesting, funding and providing genetic tests

Our finding of wide variations in the use of genetic tests between different services reflects limitation in resources as well as the fact that budgets for testing usually lie within the relatively small genetic service budget rather than within the, usually larger, mainstream budget. In nearly all services, the genetics service acted as the gate-keeper for tests, usually through a consultant clinical geneticist, and frequently also involving the use of agreed testing criteria set out by the laboratories in conjunction with UKGTN. This is particularly important for tests that are complex, and therefore expensive.

A system that requires individual agreement for genetic testing will be increasingly stretched with more clinical referrals and greater availability and utility of genetic tests. It might also become less necessary as the price of tests reduces. Discussions should be encouraged as to whether it would be more appropriate for decision-making and access to budgets for genetic testing to be held by the clinical specialty. This would enable the specialty to prioritise the use of genetic tests alongside other diagnostic methods and aspects of care within that specialty. Such a move would require:

- Contracting mechanisms that include the costs of genetic testing within the average cost envelope for referrals to that specialty
- Mechanisms to ensure the competence of those ordering and interpreting genetic tests (this should require some specialist genetic input)
- Appropriately delegated gate-keeping and authorisation of test requests by the specialty
- The continuing development, dissemination and application by UKGTN laboratories of criteria for testing in association with each test

The relative merits of budget holding for genetic tests to be by specialist genetics or clinical service require substantial discussion by commissioners and others at a national level (for example through UKGTN or GenCAG). In particular, it will not be easy to resolve the tensions

between allowing the relevant clinical services to decide their own priorities, the need to protect the limited expert services of geneticists (and not just having them acting as gate-keepers to genetic tests) and the need to protect and prioritise the limited budgets for genetic testing in UK laboratories as a whole. In particular, at a time of recession, adequate safeguards to preserve the overall spending on genetic tests should be in place before budgets are devolved to other non-genetic clinical services that may have different priorities.

5.4.3 Evaluation and regulation of genetic test provision

UK genetics laboratories receive over 150,000 samples for genetic testing each year[26]. However, in the UK as a whole there is concern that many laboratory tests are undertaken in the absence of any system to ensure clinical effectiveness and utility of individual tests. A recent Diagnostic Summit hosted jointly by the PHG Foundation and the Royal College of Pathologists recommended the establishment of a framework for evaluation and regulation of genetic tests[27].

The UKGTN, established in 2002, has a role to evaluate new genetic tests and publishes criteria for specific tests that can be available on the NHS. This is undertaken through 'Gene Dossiers' that are submitted by laboratories and assessed by UKGTN. (For further information about Gene Dossiers see UKGTN website (www.ukgtn.nhs.uk/gtn/Information/Services/Gene+Dossiers) (checked 07/10/2010)). If approved Gene Dossiers are placed in the public domain and provide some of the evidence base for clinical utility. The background concepts and methods used in the Gene Dossier process build on the ACCE Framework (**A**nalytical Validity, **C**linical Validity, **C**linical Utility and **E**thical, Legal and Social issues) and are described in the paper by Kroese *et al*.[28].

More recently, as part of the work of NICE on evaluating medical technologies, the Diagnostics Assessment Programme (www.nice.org.uk/aboutnice/whatwedo/aboutdiagnosticsassessment/diagnosticsassessmentprogramme.jsp) has been set up to focus on the evaluation of innovative medical diagnostic technologies including imaging, endoscopy and physiological measurement as well as *in vitro* tests such as blood tests. It has been agreed that UKGTN should continue with genetic test evaluations.

A significant problem, however, is that evidence particularly for rare disorders is often limited by available data especially in the domain of clinical utility and cost effectiveness. Assessment in these areas is complex and will require the establishment of patient registries and the careful follow-up of patients and families along care pathways to eventual outcomes.

5.5 Increasing skills and developing capacity in genetics in the health professional workforce

Recommendation 5

There is a need to increase the specialist workforce able to provide the specialised elements of services for inherited diseases within clinical specialties and to strengthen the supporting primary and secondary care elements.

Our reviews of both inherited cardiovascular disease and inherited eye disease acknowledge that in some areas where there is research interest or particular enthusiasm, joint genetics/clinical specialty services are working well. However, overall in the UK there is lack of capacity of appropriately specialised clinical and laboratory services with implied unmet need that, according to all the trends we have identified, is likely to increase in the future. In these and other specialties strategies will be required through continuing professional development and specialist training to build a cadre of professionals with relevant expertise in genetics aspects in the particular context of that medical specialty. Thus, those in the specialty (cardiology, ophthalmology *etc.*) need to develop expertise in genetics. For example, in cardiovascular genetics this would include professionals in cardiology, clinical genetics, genetic counselling, cardiac nursing, pathology, lipidology (including paediatric lipid care) and the associated investigative professionals such as electrophysiologists. To complement this, regional genetics services need to continue to include specialists who develop and maintain experience in this particular clinical area.

It will be necessary for leaders in each field to work with regulatory bodies, such as the Royal Colleges, and, for medical specialties, the Postgraduate Medical Education and Training Board (PMETB) to develop, where appropriate, highly specialist modules, training programmes and placements and educational resources.

For those already in post, such as, in some cases specialist nurses who may have an extended role for coordination of work with families, competence frameworks in genetics should be written, building on those developed by Skills for Health in conjunction with the National Genetic Education and Development Centre (NGEDC)[29].

In addition, inherited disease services within the various areas of medicine need to be firmly embedded in secondary and primary care services that are able to recognise individuals at risk, refer appropriately, support patients and families in interpreting and acting on specialist advice, and provide a partnership for shared care and follow-up. This requires that all professionals in that specialty, primary care, paediatrics and any of the secondary and tertiary specialties that interface with it have a necessary basic level of understanding and competence. The NGEDC has programmes to develop education in genetics for such professional groups[30].

5.6 Developing and evaluating methods for family record keeping and cascade testing that can be use within or accessed from mainstream medicine

Recommendation 6

Methods for appropriate family record keeping and cascade testing should be developed and evaluated for clinical specialties other than genetics. Unresolved questions about the sharing of data across kindreds, particularly in relation to the introduction of electronic patient records, must be addressed by policymakers through work with relevant clinicians, patient groups, and legal and IT experts.

Cascade testing for family members of patients with inherited disease is an important aspect of clinical care; it aims both to identify other individuals at risk, with instigation of surveillance or treatment and, equally importantly, to rule out increased risk for other family members, usually because they do not share a pathological mutation.

Unlike genetics services, most other clinical services have not formalised their methods for cascade testing. Activities such as family record keeping, contacting relatives, consent and sharing of genetic and clinical information within families, and using genetic test results within families to streamline the processes of testing are problematic. Although some of the current joint specialty/genetics services in the two detailed case studies undertake their entire cascade testing through the regional genetics service, those that are more embedded within the specialty (such as some of the more established London based services in the specialties examined) may undertake this work themselves, though not always in a systematic way. Whilst the routine use of regional genetics services to undertaken cascade testing may seem an obvious solution to achieving high quality, in the longer term, the predicted increase in volume of such work arising from all relevant specialties as they expand into inherited disease will challenge the capacity of genetic services, particularly genetic counselling and administration for family records.

The implementation of the NICE recommendations on cascade testing for FH has resulted in the piloting of an IT system for family cascade testing in Wales. This is an important clinical area in which the predicted volume of family follow-up required has meant that there is general agreement that it should be specialty based rather than genetics based. Interestingly, where this happens it is largely undertaken within specialist lipid services with little or no input from specialist genetics across the UK, even though the molecular genetics of the conditions and interpretation of test results can still require advice from experts. It is not yet clear how successful pilot studies for cascade testing in FH will be in identifying patients with this condition.

Systems for identifying, contacting, and advising at-risk relatives should be able to operate for a population where family members might be widely dispersed geographically and in contact with different medical services. They should be coupled with family record keeping. Plans should allow for informatics requirements including the need to share information on genetic variants for diagnostics and research and to store information in electronic patient records. The question of whether these should be ‘standalone’ for a particular condition such

as FH, more 'multipurpose' to cover a range of conditions (such as cardiovascular conditions), or generic, (for example, using the regional genetics services), should be addressed with a degree of urgency before a number of single disease 'solutions' to cascade testing and family record keeping have been initiated. Whatever the chosen model, there will be a need for expansion over and above the current systems.

At a more fundamental level for future progress, there is a difficult and still unsolved question over the sharing of data from large kindreds that may breach local data security protocols and where it may be difficult to ensure the provenance of data. These difficulties will become even more acute with the introduction of the nationwide electronic patient records in England and Wales where the scope and extent of the consents that apply to genetic information in different parts of the record (held locally and nationally) could restrict legitimate sharing. These problems must be resolved by national policy analysis and development; progress on this issue is essential if the health benefits of cascade testing are to be realised for family members.

It can thus be seen that developing an appropriate clinical response to the need for 'cascade testing' for relatives of patients with inherited disease diagnosed and cared for within mainstream services will be complex. In developing strategy it is vital that the expertise and experience of regional genetics services is harnessed, alongside experts in informatics, information technology and legal aspects of data storage and confidentiality. It may be that the regional genetics services with their established organisations and systems for family record keeping and follow-up will provide the most effective and efficient solution. In this case, they will need greatly expanded capacity to cope with the expected rise in identification of inherited disorders across the range of clinical specialties. Urgent strategic thinking and coordination of effort is now required to prevent much duplication of effort and potential incompatibility of systems and systems that are unduly restricted because of failure to address basic legal requirements for data protection.

5.7 Development and evaluation of models for integration of genetics in other clinical specialties

Recommendation 8

Models should be developed to ensure effective and efficient provision of specialist genetic support to other clinical services.

With expansion of knowledge and capability for new applications in inherited disease, specialist genetics input into the diagnosis and care of patients and families within the various clinical specialties will increase in importance. There will be a need for expansion of capacity and expertise within clinical and laboratory elements of the genetics services to support this development. Genetic counsellors may play a key role in providing the genetic input into other clinical areas whilst maintaining liaison with the regional genetics service. As the volume, breadth and complexity of work expands regional genetics departments will play key leadership roles in shaping clinical pathways where inherited conditions or technologies involving molecular genetics are significant features.

Models for the provision of such care should be developed and evaluated. Important parameters for such models, however, must include:

- Recognition that the overall capacity of clinical genetics input will be limited (albeit that there may be some modest increases), given the expanding breadth of services they will be required to support
- Commitment to the development of capabilities, competences and supporting systems to allow some of the traditional roles of regional genetics services to be undertaken by mainstream health professionals within other clinical specialties.

As a support to emerging models there needs to be further developmental and strategic work at a national level to agree:

- The elements of care that should be provided by specialist genetics (examples are set out in Box 6)
- The elements of care that could be provided by the mainstream services themselves
- The general organisational support that regional genetics services should provide to the service (for example education, mentoring, formulation and support of ethical practice, systems for consent, family follow up and family record-keeping).

Box 6 Specialised elements of care that should be provided by specialist genetics services

- Detailed examination of family history with capacity to verify diagnoses through family and other records
- Identification of dysmorphic and other features associated with rare genetic syndromes
- Assistance with molecular diagnosis through detailed knowledge of possible molecular pathology, likely utility of genetic testing and assistance in interpreting uncertain results
- Advice about recurrence or counselling about prenatal testing
- Access to systems for family record keeping and undertaking family follow-up
- Advice on ethical, legal and social issues such as consent, confidentiality and issues related to ethically difficult areas such as testing of children, pre-implantation genetic diagnosis, prenatal testing, termination of pregnancy, dealing with unexpected results, when and how to contact relatives *etc*.
- Education, training, mentoring and supervision of genetics elements of services.

On a practical level, the various current models for the interaction between genetics and other specialist services should be examined and evaluated. These are in place within various clinical contexts involving inherited disease and include such elements as specialist clinics, joint clinics, parallel clinics, multidisciplinary meetings, tele-links, ward rounds, email discussions, liaison meetings and the use of genetic health visitors.

5.8 Building audit and research programmes to evaluate effectiveness and cost-effectiveness of services

Recommendation 7

Audit and research programmes to evaluate effectiveness and cost-effectiveness of services should be developed. This is vital in a climate where health services will need to be prioritised and recognises the current paucity of evidence about the overall effectiveness of specialised services and genetic testing in improving outcome for patients and family members.

Specialist services in these developing areas need to remain aware of the need to compete in an environment where resources for healthcare are stretched and developments able to demonstrate cost effectiveness for patient benefit will be prioritised. There will be demands for evidence that specialised services for patients and families with inherited disorders lead to enhanced outcomes. Audit and research are thus vital aspects in the development of high quality services for inherited conditions within mainstream medicine.

Many services will be starting from a very low baseline of provision and so it is vital that a monitoring and audit programme is set up to track provision and activity. Initial steps will be to build on agreed standards and develop methods for benchmarking inherited conditions services.

As cascade testing programmes are developed for different inherited conditions within the services it will be essential to monitor outcomes, to ensure that the clinical benefit to family members who are invited to take up the offer of testing outweighs any physical or psychosocial harm resulting from anxiety related to (possibly unwelcome) knowledge about risk, diagnosis and treatment.

As more basic research garners understanding about the molecular basis of inherited disease and increases capabilities to undertake genetic testing and provide preventive and treatment options, there will be a need for careful translational research to ensure that they are put to best use for patient benefit. Current assumptions, for example, on the management of symptomatic patients cannot necessarily be applied to asymptomatic individuals discovered by cascade family testing, or to individuals with similar clinical manifestations but different underlying molecular abnormalities (phenocopies). Fine tuning clinical management will depend on careful research that identifies and investigates natural history and outcomes in cohorts of patients that pass through the expert services for inherited disease (such as specialised inherited cardiovascular conditions services) and other service provision.

Important areas for research include:

- Epidemiological work to provide information on disease incidence and prevalence
- Genotype-phenotype correlations
- Natural history of disease including genotypic sub classifications

- Effectiveness of interventions including genotypic sub classifications
- Development and evaluation of methods for family cascade testing.

Such studies will be essential to support future arguments for prioritisation of services for people with inherited conditions.

6 Discussion and conclusions

Between 2006 and 2009, the PHG Foundation carried out needs assessment and service reviews of two clinical areas in which the diagnosis and management of people with inherited disorders is an important clinical activity. This work was in direct response to the Department of Health strategic vision that genetic services would become 'more mainstream' within the NHS. It focused on two specialties where management of patients with inherited disorders constituted an important subset and asked, firstly about need for services and, secondly, about the capacity and nature of these services. Preliminary conclusions relevant to these two case studies were then projected into a future consideration of health services where parallel developments in diagnosis and management of inherited disease in many other clinical areas was envisaged. This paper results from this wider consideration and is informed also by consultation on the preliminary paper organised by the UKGTN.

An immediate concern in relation to the two specialties examined is the concept of 'mainstreaming' genetics. Although there are increasing numbers of genomic based tests that may influence clinical management and,in the future prediction of complex disease may become important, the main focus for this work was the care of people with single gene disorders. This remains a complex and specialised area and not one that every service should provide. At present it is not an appropriate area for mainstream services, in the sense that 'all district or general cardiology or ophthalmology services should be doing it'. However, these services need to be able to identify patients who may have these conditions and refer appropriately to more specialised inherited disease services; only to that extent is genetics a 'mainstream' issue.

With regard to the specialties examined a number of services throughout the UK have responded to the increasing availability and clinical utility of genetic tests. In many cases the main initiative has been from genetic services, which have set up 'joint' genetics services with the clinical specialty. These services have mostly been led and provided by clinicians with a particular research interest, with the result that there is gross inequity of provision across the UK. Moreover, with scarce resources for service development, the overall clinical capacity and quality is extremely patchy.

From our detailed examination of need, based on epidemiology, anticipated clinical utility, patient demand and desirable clinical quality we suggest that the need for such specialised services for inherited disorders will continue to increase rapidly in the future. Similar issues are evident in other specialties. In the consultation the range of services mentioned included neurology, cancer and oncology, cleft specialists, prenatal, fetal and maternity services, paediatrics, haematological malignancy, haemoglobinopathy services, haemophilia, thrombophilia and a range of other inherited blood disorders, bone marrow transplantation. This list is not exhaustive.

A number of different models operate for the provision of services in which genetics and other mainstream clinical elements are both key elements. We suggest that the future pattern of care may be one in which clinical services outside clinical genetics encompass inherited aspects in a variety of ways and the necessary specialist clinical and laboratory elements are integrated through commissioning of the various appropriate clinical pathways. This raises a number of issues in policy development including those related to commissioning, equitable service development, developing networks, genetic test provision and mechanisms

for requesting, funding and providing them, increasing skills and capacity in the professional workforce, methods for cascade testing and family records, audit and research, and the different models for provision of specialist genetics support within mainstream services.

In addition to the proposed role for specialist genetics in supporting the management of inherited disorders within other clinical specialties, the rise in use of technologies in other areas of laboratory medicine documented in the House of Lords *Genomic Medicine* Report, particularly oncology, pharmacology, microbiology and transplantation support raises the issue of molecular genetic support to these laboratories and suggests a further important interface for the Regional Genetics Services.

The necessary policy developments to match new needs with new capabilities amount to a major service development that integrates elements of clinical and laboratory genetics in many areas of clinical practice. Clinical and laboratory geneticists and genetic counsellors with their special knowledge of basic science and clinical management of families, and their comprehensive experience of the many ethical, legal and social aspects are an invaluable asset and will be essential in leading and supporting this service development.

Vital also will be the leadership of commissioners, public health specialists, other clinicians and voluntary organisations helping to implement such changes.

Finally, at a time of major change in NHS structures and arrangements, it will be important that the momentum for development is maintained – a role that will inevitably fall to the relatively small number of champions in provider services and research.

Service development has been designated by the Human Genomics Strategy Group, set up by the Government in response to the House of Lords *Genomic Medicine* Report, as one of three key strategic areas for genomics in the UK to be undertaken by the sub-committees. The eight strategies identified in this paper will be key to ensuring that UK NHS services are properly positioned to take advantage of new genomic technologies effectively, efficiently and equitably for the benefit of population health.

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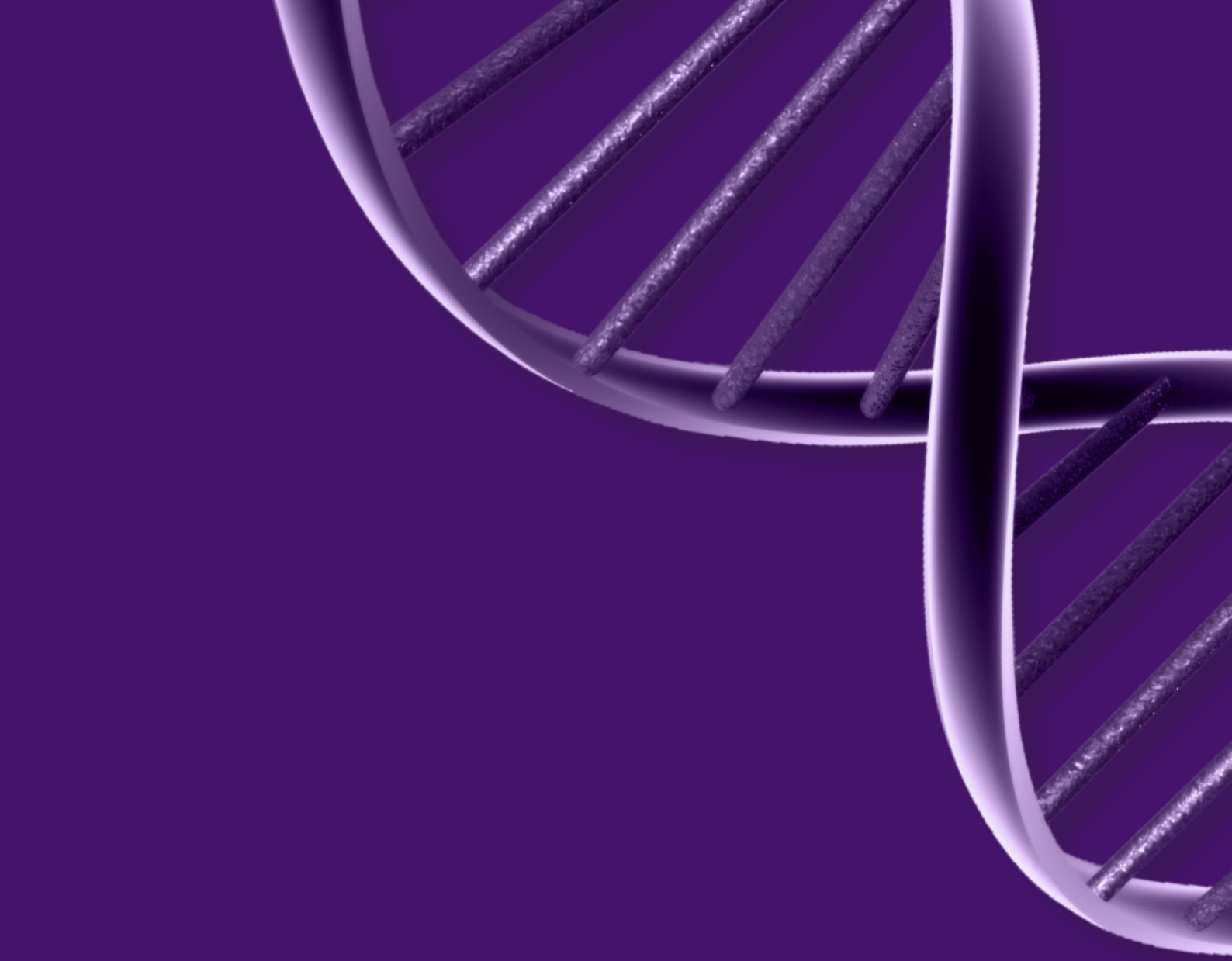
The PHG Foundation is a forward-looking policy think-tank and service development NGO based in Cambridge, UK. Our mission is *making science work for health*. We work to identify the best opportunities for 21st century genomic and biomedical science to improve global health, and to promote the effective and equitable translation of scientific innovation into medical and public health policy and practice.

We provide knowledge, evidence and ideas to stimulate and direct well-informed debate on the potential and pitfalls of key biomedical developments, and to inform and educate stakeholders – policy makers, health professionals and public alike. We also provide expert research, analysis, health services planning and consultancy services for governments, health systems, and other non-profit organisations.



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