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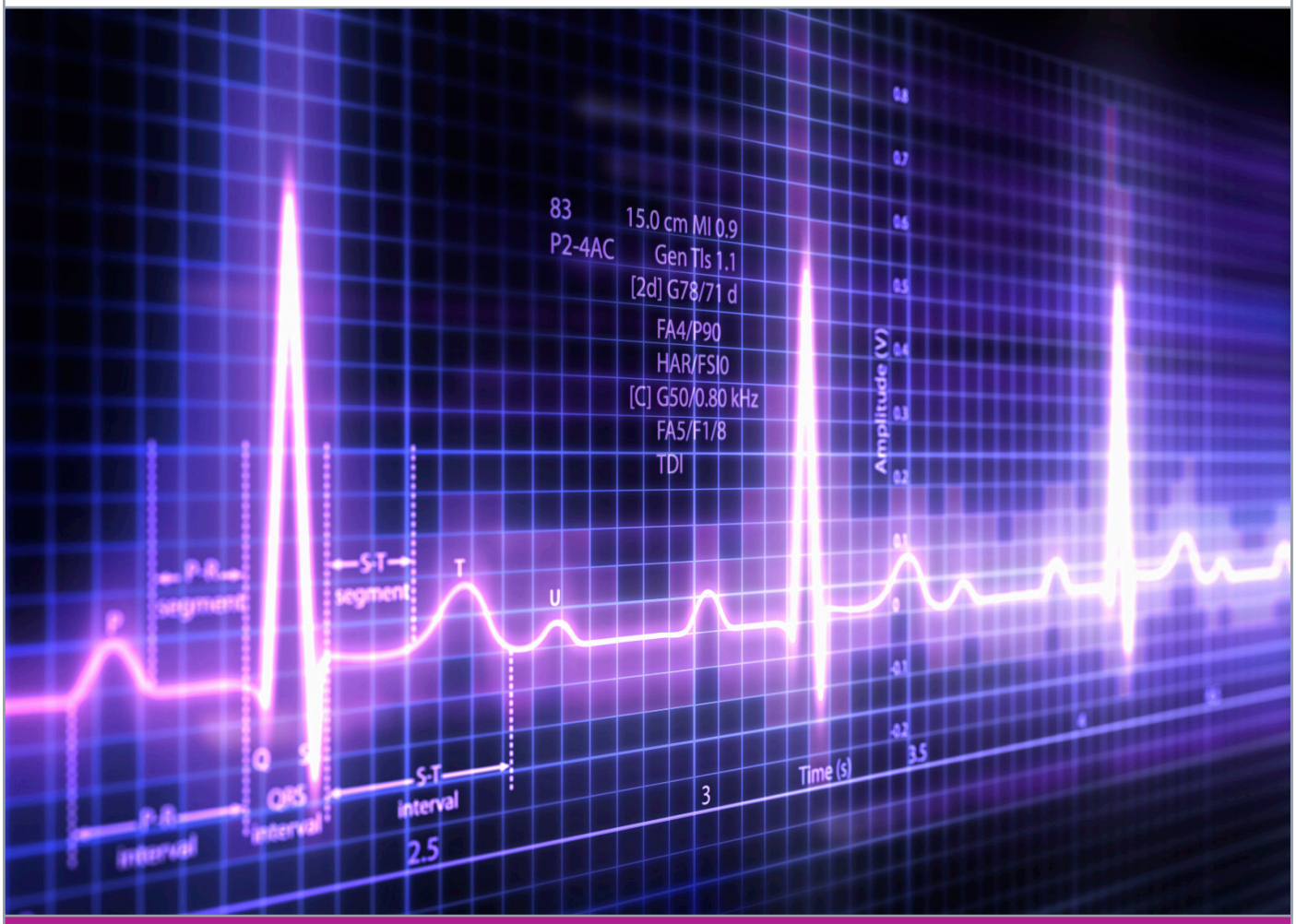
Heart to Heart

Inherited Cardiovascular Conditions Services

A Needs Assessment and Service Review



Hilary Burton
Corinna Alberg
Alison Stewart

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PHG Foundation Team

Dr Hilary Burton	Programme Director
Ms Corinna Alberg*	Project Manager
Dr Alison Stewart	Principal Associate

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Cambridge
CB1 8RN
UK
Tel: +44 (0) 1223 740200
Fax: +44 (0) 1223 740892

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** To whom correspondence should be addressed:*
corinna.alberg@phgfoundation.org

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Foreword

Professor Peter Weissberg

Medical Director

British Heart Foundation

This document is the product of a huge amount of hard work involving almost everyone in the UK with an interest in Inherited Cardiovascular Conditions (ICC). The findings of the Working Group illustrate what happens when clinical services evolve organically around specialists with a particular interest. Centres of excellence emerge, but not necessarily in the right places, and there is commonly a gross geographical mismatch between service provision and population need. This is typical of an embryonic specialty driven mostly by research orientated clinicians. However, as a consequence of the ongoing and rapidly advancing revolution in genetics, ICC has now come of age. Many of the causative genetic mutations are known and, in many cases, effective treatments are available. Therefore, it is no longer acceptable for someone at risk of an ICC not to receive timely, expert attention.

The review contains exemplars of the multidisciplinary approach needed to provide an appropriate service for patients with ICC. As we move into an era of World Class Commissioning it behoves commissioners to pay attention to this document and ensure that there is equity of access to first class specialist services across the UK for all patients suspected to be at risk of an ICC. The BHF is delighted to be partnering the Department of Health in launching a genetics information service that will ensure that relatives of a victim of a presumed ICC will be provided with all the information they need to access appropriate care, advice and support from the health service and other relevant support groups.

Review of Services for Inherited Cardiovascular Conditions - Executive Summary

Inherited cardiovascular conditions (ICCs) are a group of monogenic disorders primarily affecting the heart, its conducting system or vasculature. In some cases, the first indication that an individual has an ICC is sudden cardiac death (SCD), often in adolescence or early adulthood. When an ICC is diagnosed, or suspected, there are implications for the individual's relatives, who may also be at risk.

Two surveys of service provision for ICCs, undertaken in 2006, highlighted variation in service provision but noted that a more comprehensive review was warranted. The Foundation for Genomics and Population Health (PHG Foundation) was invited to undertake a needs assessment and review of ICC services under the supervision of an expert Working Group.

This project is intended to inform the work of commissioners and providers charged with implementing Chapter 8 of the National Service Framework for Coronary Heart Disease (2005), which makes key recommendations for the provision of services for patients and families with SCD and ICCs. It was agreed also to include familial hypercholesterolaemia (FH) within the scope of this review, as this relatively common monogenic disorder is associated with premature coronary heart disease.

Science, epidemiology and clinical management

The last decade has seen dramatic advances in our understanding of the molecular pathology of ICCs. More than 50 ICCs have been recognised and genetic tests are increasingly available for the more common disorders (such as FH and hypertrophic cardiomyopathy (HCM)) and for some rarer disorders (for example, Marfan syndrome and long QT syndrome (LQTS)). The conditions are highly heterogeneous, both genetically and clinically.

Epidemiological evidence is incomplete, but suggests a combined total prevalence for ICCs of about 340,000 in the UK (including approximately 120,000 individuals affected by FH). Risks associated with the conditions are highly variable, depending on the mutation and the spectrum of clinical risk factors. The average annual risk of SCD is about 0.1% for LQTS, and the annual mortality for HCM about 0.3–1%. Risks are substantially higher for patients with the most severe symptoms or in those who have experienced a resuscitated cardiac arrest. Mutation carriers with no identifiable clinical risk factors have lower absolute risks. For FH, annual average mortality is about 0.1–0.5%. Marfan syndrome can be fatal by age 30 or younger if untreated.

For many ICCs, careful clinical management can reduce risk. For arrhythmia syndromes (such as LQT) and HCM, treatments can include a variety of drugs, lifestyle advice to avoid triggering events, fitting of implantable defribillator devices or, in some cases, surgical options. FH can be successfully treated by statins.

Genetic testing can aid clinical management by enabling more accurate diagnosis and risk assessment, and in some cases guiding the choice of treatment. Importantly, identification of a mutation in an affected person enables their relatives to be offered targeted testing for the same mutation. Those who carry the mutation can then be assessed and offered appropriate surveillance and/or treatment, while those who do not carry the mutation can be spared further investigation. This approach is known as cascade testing.

Along with genetic discoveries have come advances in specialist branches of cardiology, such as electrophysiology, echocardiography and imaging techniques, that have improved and refined diagnosis and management of ICCs. The conditions are extraordinarily varied and complex, requiring specialist input at almost every stage of diagnosis and management.

Policy background

Policy initiatives, particularly Chapter 8 of the National Service Framework for Coronary Heart Disease and England and Wales (and a similar initiative in Scotland) have mandated improved services for ICCs, focusing initially on the arrhythmia syndromes and HCM but more recently broadening in scope to include a wider range of ICCs. For FH, guidance issued by NICE in 2008 recommended systematic cascade genetic testing in the extended families of affected individuals.

Initiatives by professional groups (for example, Heart Rhythm UK) and the charitable sector (for example, the British Heart Foundation and patient-representative groups) have raised awareness of ICCs and supported improved recognition and management of families affected by SCD.

Policy initiatives described in this report relate primarily to England and Wales but are of relevance to how services are developing in Scotland and Northern Ireland.

Patients' perspective

Despite the recent policy impetus, a focus group of representatives of patient-support groups, convened as part of our review, concluded that services are still inadequate to deliver a timely, coordinated and holistic service to patients and their families. Awareness of ICCs among coroners, GPs and general cardiologists is still too low, with the result that patients may not receive appropriate referral to the specialist service. Access to genetic advice and testing was seen as problematic, with insufficient communication between specialist genetics and cardiology elements of the service. Patients would like to see better continuity of care, with improved liaison between the specialist service, local cardiology clinics and GPs.

Review of services

A questionnaire sent to all regional genetics centres identified 18 services specifically for ICCs and 2 Marfan services. Four respondents indicated that their area did not have such a service, but in two this was under development.

Services were asked to provide both qualitative information about service configuration, operation and resourcing, and quantitative information about activity levels including number of clinics per month, staffing levels, total numbers of patients seen, numbers of new referrals, and numbers and types of genetic tests performed. Services were asked to note any gaps or deficiencies in their provision.

The two main conclusions from our survey are that overall in the UK the capacity of services is inadequate to meet either current or future estimated needs, and that service provision is highly unequal in quality as well as quantity across the country. Estimates based on extrapolation from current service provision suggest that services would need to see an additional 7,000 new patients per year to bring the most poorly provided services (mostly in the regions) up to the level of the best. Epidemiological data suggest that the true shortfall may be significantly higher and that it will be likely to increase as more genetic tests become available and cascade testing gathers pace.

All the measures of activity surveyed suggest significant inequity in service provision across the country, with typically 10- to 20-fold variation between the best and worst provision. The wide variation in use of genetic tests is of particular concern, given the growing number of tests available and the importance of a genetic diagnosis for cascade testing.

Services are highly London-centred. 59% of outpatient clinics, staffed by 60% of the medical consultant sessions in the UK, take place in London, representing a six fold greater per capita level of service provision than the rest of the UK overall.

An independent survey of lipid clinics serving patients with FH, carried out by HEART UK and summarised in our report, also notes wide variation across the country and highlights, in particular, deficiencies in genetic elements of the services and in appropriate provision for management of children and young people with FH.

What makes a specialist service?

An effective specialised service for ICCs must be capable of providing or organising care for the full range of these complex, variable conditions in a timely and integrated fashion. It should include a full range of clinical professionals (consultants in cardiology (adult and paediatric), genetics, genetic counselling, specialist nursing, laboratory science and pathology) as well as investigations including specialised imaging technologies, electrophysiological studies and exercise testing.

Qualitative analysis of information collected by our survey indicates that there is inadequate provision for some conditions within existing services. In addition, while most services include an effective range of professional roles, they are often not working as a truly multidisciplinary team. The relative weight given to different areas of specialist expertise is variable and, in many services, genetics and cardiology elements of the service operate in parallel.

Our survey findings suggest that, although the methods and mechanisms of cascade testing are firmly established within clinical genetics, they are less familiar within cardiology and that systematic cascade testing is not always a routine part of family management.

Many services recognised deficiencies in their referrals and the need for better outreach to GPs, local cardiology clinics and the coronial service. The need for a more proactive approach to achieving geographic and socioeconomic equity of access was also acknowledged.

Our survey revealed a number of models for ensuring that the service was provided across a whole population. Successful models included a ‘hub and spoke’ model in which tertiary activities were concentrated in one or a small number of central facilities, with less specialist aspects of care devolved to district cardiology services; and models involving development of ‘satellite’ specialised clinics, sometimes in order to provide care in more remote areas.

The complementary roles of commissioners and cardiac network managers are critical to the provision of high quality, secure and stable services to a population. Our survey findings indicate that most current services have not been established formally as specialised ICC services operating within the cardiac network and so have not been formally commissioned.

All services should have a clear statement of the purpose of the service and the outcomes it is designed to achieve. Our survey findings show that formal descriptions of the service, its objectives, components and standards are not in place for most services.

Ethical and legal issues

An expert subgroup was convened as part of this project to address the ethical and legal issues that arise when a suspected or definitive diagnosis of an ICC is made, either in a person who has died suddenly or in a living patient. The Group particularly noted current barriers to the effective care of families affected by ICCs.

The familial nature of ICCs means that it is often necessary to use tissue and genetic and clinical information about an affected person for the benefit of another family member. There is a lack of clarity over the legal status of samples taken under the Coroner’s authority for investigating the cause of a sudden unexplained death. The current default regime is that such tissue samples are destroyed once Coroner’s authority lapses, if family members fail to consent to ongoing retention as mandated

by the Human Tissue Act. The lack of coherence in the legal framework affecting such samples has created a fragmented service which means that at-risk families are not receiving optimal care.

Under the Data Protection Act and other legislation, consent is also required for the use of medical data about a living person for the benefit of a relative. The cascade approach requires the linking of genetic information about an extended family – a practice that is familiar within genetics services but less so in cardiology. More research is needed on the range of practices in current use in clinical genetics, cardiology and lipid clinics, and on how different systems can be rationalised to better serve the needs of families. There is also a need for further research to establish best practice for informing the relatives of the index case that they may be at risk, and how to proceed when difficulties arise within families.

Substantial improvements to IT systems will be needed if cascade programmes are to be feasible. The need to collate and integrate data from a number of different NHS Trusts, whilst ensuring that the provenance of data remains clear, and patient choices regarding sharing of their data are recorded and respected, exceeds the capabilities of existing systems.

For some ICCs, evidence is accumulating that diagnosis and initiation of treatment during childhood or adolescence can improve outcomes. However, there may be debate about where the balance lies between clinical benefit from early initiation of treatment, and respect for the child's autonomy.

Horizon scanning

New genetic technologies such as next generation sequencing and array comparative genomic hybridization (array CGH) will revolutionise the genetic diagnosis of highly heterogeneous conditions such as ICCs by enabling testing for multiple mutations in multiple genes. It is important that policy makers and commissioners recognise and prepare for these dramatic changes that will occur in the next 3-5 years. Improved understanding of the molecular pathology of ICCs can also lead to new therapeutic possibilities. An example is a potential disease modifying agent (Losartan/Irbesartan) for Marfan syndrome.

Some technologies (such as array CGH) are already in clinical use and some pharmacogenetic applications are ready for clinical evaluation. Recommendations for inclusion of new tests in the NHS portfolio need to be made on a case by case basis to practitioners and commissioners, based on the results of translational research.

Recommendations

The speed of advancing basic science and development of clinical applications in inherited cardiovascular disease make it imperative that an infrastructure of clinical services is developed now, and that deficiencies in current services are addressed.

Based on the findings of this review, the Working Group made 16 recommendations.

ESTABLISHING A STRATEGY

Recommendation 1

Each cardiac network should ensure that its population has access to specialised expert ICC services for children and adults. The scope of ICC services should include:

- inherited arrhythmia syndromes (including SADS)
- cardiomyopathies, including cardiac manifestations of muscular dystrophies
- inherited arteriopathies (for example Marfan syndrome)
- disorders of cholesterol metabolism that cause coronary atherosclerosis.

Recommendation 2

Most cardiac networks should not seek to develop their own ICC service. However they should ensure their population has access to a full range of services that meet agreed standards. Cardiac networks and those responsible for them at a national level should discuss and agree an indicative size, number and distribution of services. Because of the need to concentrate development and to ensure critical mass, the Working Group recommends that a relatively small number of services are supported in the UK (probably around 10 services outside London). In order to ensure that current expertise is not lost, where services are in close proximity, this might best be achieved by consolidation and integration of services.

Recommendation 3

Across the UK providers and commissioners of ICC services should anticipate and plan for a steady increase in demand within the next 5 to 10 years. In many areas this may require an expansion of several-fold to cope effectively and equitably with the needs of patients and families.

Recommendation 4

An Expert Advisory Group should be established to guide and provide expert input for major strategic development. It should be multidisciplinary and include the perspectives of commissioners and voluntary organisations. In order to make significant progress the Group should include a small number of lead clinicians, public health professionals and administrative staff with dedicated time and should have resources to undertake a modest programme of stakeholder engagement, travel and other related activities.

COMMISSIONING

Recommendation 5

Formal and explicit commissioning mechanisms for ICC services should be developed by the cardiac networks in collaboration with commissioners of cardiac services and specialised commissioners for genetic elements of the services. These should reflect the need to provide high quality expert services balanced against reasonable geographic accessibility and should conform to the aspirations in World Class Commissioning.

Recommendation 6

Cardiac networks should commission an ICC Commissioning Framework via the Expert Advisory Group. This framework will give quantitative and qualitative guidance on the services that should be provided and their integration with primary, secondary and other specialised services.

Recommendation 7

Professional groups should take the lead in developing and agreeing a set of standards for specialised ICC services. This would include a description of the required skills and facilities, indications of expected activity, organisational aspects, audit and research. The specification should include a minimum immediate standard.

Recommendation 8

Cardiac networks should ensure that, by service developments, local consolidation and collaborative mechanisms, the ICC service for their patients sets out a realistic plan for reaching agreed standards within an appropriate timeframe. Services that do not currently reach minimum standards should not be characterised as ICC services.

EDUCATION

Recommendation 9

Professionals from the range of ICC services should work with appropriate professional organisations, regulatory bodies, educational institutions and providers of specialist training to develop a workforce with the necessary specialist competences in the clinical, laboratory, pathology and allied professional groups. This should include continuing professional development and higher specialist training.

Recommendation 10

Professionals from the ICC services should work with the National Genetics Education and Development Centre to develop educational resources to improve competences in inherited cardiovascular disease in professional groups involved in primary, secondary or other specialist elements of care for ICC patients.

ENHANCING AND MONITORING THE EFFECTIVENESS AND EFFICIENCY OF SERVICES

Recommendation 11

ICC services should collaborate on the development and evaluation of systems of cascade testing in conjunction with regional genetics services including the development of IT systems that can link individuals within families.

Recommendation 12

Systems need to be developed to ensure the appropriate retention of samples following sudden cardiac death, the promotion of best practice regarding consent and data sharing within clinical practice, and effective approaches to cascade testing. The responsibility of coroners to family members who may be at risk of sudden cardiac death requires clarification and strengthening. Each of these measures may require legislative change.

Recommendation 13

The Genetics Commissioning Advisory Group (GenCAG) through the UK Genetic Testing Network (UKGTN) should undertake a review of laboratory provision and finance to ensure effective, efficient and equitable genetic test provision in the light of current test availability and likely future developments in testing technology. It is anticipated that this might involve recommendations to consolidate laboratory provision of ICC genetic tests in a small number of laboratories around the UK.

Recommendation 14

ICC services should set up coordinated audit programmes to evaluate service provision, activity and outcomes against agreed standards. It is envisaged that patient activity will be captured through national database systems such the central cardiac audit database, heart failure database, pacing database and SADS database.

TRANSLATIONAL RESEARCH

Recommendation 15

ICC services should collaborate in setting up research programmes designed to investigate disease incidence, prevalence, genotype-phenotype correlation, natural history and the evaluation of clinical care. It is envisaged that these studies will be facilitated by the setting up of a national case register.

Recommendation 16

Clinical and laboratory experts within the ICC services should maintain an overview of emerging technologies and novel tests and work with research institutes, NHS Trusts, public health, patient groups and other relevant organisations to ensure that translational research programmes are set up which critically evaluate the clinical utility of such technological developments, consider the implications for clinical practice and ensure timely implementation into service provision.

Chapter 1 Introduction and background

1.1 Introduction

Most heart disease in the population is caused by environmental and lifestyle factors, such as smoking or poor diet, interacting with genetic predisposition. The genetic variants underlying such multifactorial heart disease are thought to be common variants that are individually modest in effect.

In some individuals, however, heart disease may be caused by a single genetic mutation that strongly increases risk. Inherited cardiovascular conditions (ICCs) are a group of monogenic disorders primarily affecting the heart, its conducting system or vasculature. The individual mutations causing these conditions are rare or relatively so, but collectively the conditions represent a significant burden of mortality and morbidity in the population. In some cases, the first indication that an individual has an ICC is their sudden death, often in adolescence or early adulthood. Sudden cardiac death (SCD) or a serious cardiac event in an otherwise healthy young person raises the possibility of an underlying genetic condition and suggests that their relatives may also be at risk.

In late 2006, at the British Society of Human Genetics meeting in York, a group of 22 interested clinicians (primarily clinical geneticists and genetic counsellors) met to discuss the establishment of a United Kingdom Cardiac Genetics Network with the aim of improving service provision for the diagnosis and management of ICCs. Two surveys of service provision undertaken in 2006 highlighted variations in these services (Brennan 2006, Heart Improvement Programme 2006, unpublished survey) although the group noted that a more comprehensive service review and needs assessment was warranted in the light of their findings. The group proposed that the Foundation for Genomics and Population Health (PHG Foundation, formerly the Public Health Genetics Unit) should be invited to undertake this work, under the supervision of an expert Working Group, by providing a comprehensive needs assessment and review of cardiac genetics services that also includes the prevention and management of SCD.

This report of the work undertaken is intended to inform the work of commissioners and providers charged with implementing Chapter 8 of the National Service Framework for Coronary Heart Disease (Department of Health 2005), which makes key recommendations for the provision of services for patients and families with SCD and ICCs.

Following discussions with the Department of Health (DH) and Professor Steve Humphries, it was also agreed to include familial hypercholesterolaemia (FH) within the scope of this review, as this relatively common monogenic disorder is associated with premature coronary heart disease, which often also presents as SCD. In addition, a pilot project to audit and implement cascade testing for FH within affected families is relevant to potential initiatives to undertake cascade testing for other ICCs and SCD conditions.

1.2 Aims

The primary aims of the Working Group were:

1. To make recommendations for the development of ICC services which meet the requirements of service commissioners and providers, health care professionals, and patients and their families.
2. To strengthen and complement the service developments arising as a result of the implementation of Chapter 8 of the National Service Framework.
3. To inform a strategy for the development of ICC services in the UK and develop a programme for its implementation.

1.3 Scope of the work

The scope included both single gene disorders that primarily affect the heart and those with cardiovascular manifestations, but excluded common multifactorial cardiovascular disorders (such as coronary artery disease) and their risk factors (such as polygenic hyperlipidaemia).

1.4 Objectives

1. To review the epidemiology of single gene disorders that increase an individual's risk of cardiovascular disease (for example, those causing HCM, LQT, FH and Marfan syndrome).
2. To review the contribution of these disorders to mortality.
3. To review availability of and access to clinical and molecular testing for these disorders.
4. To summarise available evidence on the evaluation of genetic tests through review of recent literature and use of informal networks.
5. To review the availability and use of evidence-based clinical guidelines.
6. To review pertinent ethical and legal issues, primarily those of sharing genetic data and obtaining and storing human tissue.
7. To quantify the likely need and demand for services for people with ICCs, including the impact on workload of cascade testing in families.
8. To describe key elements of ICC services including diagnostic processes, specialist genetics elements, complementary specialist cardiology and paediatric services, links with closely related services such as Grown Up Congenital Heart (GUCH) services and familial hyperlipidaemia services, and those elements that need to be in place in primary care, secondary care, pathology and coroner services and the pathways and connections between them.
9. To receive patients' perspectives on inherited cardiac disease services.
10. To review current specialist genetic input into cardiac services and cardiac input into genetics services including sudden cardiac death, arrhythmias and other inherited cardiovascular conditions with the aim of providing equitable, high-quality services in future designated specialist centres.
11. To assess different models of specialist service provision, such as dedicated multidisciplinary clinics and the role of specialist nurses, genetic counsellors and other health care professionals.
12. To develop a commissioning framework and service specification for ICC services.
13. To review the availability of high-quality information for patients and their families and make recommendations.
14. To scope current and future technological developments that are likely to have an impact on cardiac genetics services and consider the implications for strategic planning.
15. To provide a report to the Heart Improvement Programme and to disseminate the report to other interested organizations.

1.5 Methods

The work was undertaken by a project team from the PHG Foundation, assisted for individual parts of the project by members of the Working Group. The PHG Foundation provided project management (Corinna Alberg), public health consultancy and overall leadership of the project (Hilary Burton), epidemiological analysis (Simon Sanderson, Gurdeep Sagoo and Alison Stewart), legal and ethical analysis (Alison Hall) and administrative support (Jane Lane). Alison Stewart took the lead role in writing and editing the project report.

The Working Group, chaired by Hilary Burton, included experts from cardiology, clinical genetics and laboratory genetics, together with representatives from specialised commissioning, cardiac networks and patient support groups. Some members of the Working Group, together with other co-opted

experts, formed a subgroup charged with investigating and analysing the ethical and legal issues associated with the diagnosis and management of ICCs in patients and families. Another meeting was held with members of the Working Group and other experts on FH to examine relevant issues concerning FH that should be included in the report. A focus group meeting was held to elicit patients' perspectives on ICC services.

The project took place between November 2007 and February 2009. During that period, the Working Group met 5 times. The meetings were used to:

- agree terms of reference
- discuss and agree likely sources of data
- receive expert input from professional and voluntary sectors
- design, undertake and assess a review of current services for ICCs
- review emerging analysis and evidence and discuss further requirements
- consider and agree final recommendations
- gain ownership of the final Report amongst a wide stakeholder group

The Report is in 9 chapters:

Chapter 1 sets out the background to the project, the terms of reference and the methods.

Chapter 2 summarises recent advances in scientific understanding of ICCs, together with the available epidemiological evidence concerning their associated mortality and morbidity. Elijah Behr provided valuable input to the epidemiological analysis. The chapter also presents case studies, contributed by Elijah Behr and Hugh Watkins, that illustrate the complexity of the diagnostic and management processes, supporting the need for an integrated multidisciplinary specialist service. Parts of this chapter were written by Alison Stewart, Simon Sanderson and Hilary Burton.

Chapter 3 summarises and discusses recent clinical and other policy developments relating to the recognition and management of ICCs, particularly when there has been a sudden cardiac death. This chapter was written by Simon Sanderson and Alison Stewart.

Chapter 4 discusses ICC services from the patient's point of view, outlining patients' priorities for services, their perception of current gaps and other aspects needing improvement. This chapter takes the form of a report, written by Alison Stewart, of a focus group meeting comprising representatives from several patient support groups.

Chapter 5 presents a summary of our review of current services, including geographic coverage, capacity in the different specialties, structure of the services, activity, and use of genetic tests. The service review was conducted and the chapter compiled by Corinna Alberg.

Chapter 6 presents the case for strengthening and developing ICC services as multidisciplinary specialist services. Descriptions of the specialist roles and resources needed are supplemented by discussion of the optimum models for the structure and function of the service, including access to and use of genetic testing. The discussion and conclusions are supported by highlighted findings from our service review. The Chapter was written by Hilary Burton and Alison Stewart, using input from several members of the Working Group who provided information about specialist roles.

Chapter 7 discusses some of the ethical and legal issues associated with the diagnosis and management of patients and their families. The focus is on issues surrounding the sharing of data and tissue samples within families (particularly the current legal requirements for consent), and among health

professionals charged with providing optimal care for the whole family. The chapter, prepared by Alison Stewart, is a shortened and adapted version of a longer paper written by Alison Hall and members of a subgroup formed for this part of the project.

Chapter 8 discusses new technological developments in genetics and cardiology that are likely to have a major impact on clinical services for ICCs. The chapter was written by Jenny Taylor.

Chapter 9 sets out the Working Group's recommendations for development of specialist services for ICCs, to provide optimal care for patients and families affected by or at risk of these conditions.

An Executive Summary summarises the major findings and recommendations of this report.

A set of Appendices provides more detailed information about the epidemiology of ICCs, current ICC services including genetic testing and membership of the working group.

Chapter 2 Science, epidemiology and clinical management

2.1 Introduction

The last decade has seen dramatic advances in our understanding of the molecular pathology of ICCs. Genetic approaches have successfully defined the molecular basis for an increasing number of these conditions, such as hypertrophic cardiomyopathy (HCM) and Brugada syndrome (reviewed by Noseworthy 2008; online reviews for individual conditions may also be found in GeneReviews). More than 50 ICCs have been recognised and genetic tests are increasingly available for the more common disorders (such as FH and HCM) and for some rarer disorders. Along with genetic discoveries have come advances in specialist branches of cardiology, such as electrophysiology, echocardiography and imaging techniques, that have improved and refined diagnosis and management of these conditions. Greater knowledge has also brought with it the realisation that these conditions are extraordinarily varied and complex, requiring specialist input at almost every stage of diagnosis and management.

2.2 Scientific background

The contraction of the heart is a complex biochemical and electrophysiological process that involves the synchronised contraction of each of the millions of cardiac myocytes, or heart muscle cells. The synchronisation is achieved by a specialised conducting system mediated by ion-conducting pumps and channels in the myocyte cell membranes. These pumps and channels are composed of proteins that form pores whose opening and closing is coordinated by electrical signals. When the cells are stimulated to contract, flows of sodium, potassium and calcium ions through the channels generate an 'action potential' in the cardiac myocytes and propagate the signal to contract through the neighbouring cells. The action potential causes the release of calcium from intracellular stores within the cardiac myocytes. The calcium ions act on subcellular structures called myofibrils, which consist of alternating filaments of the muscle proteins actin and myosin, together with other proteins. Calcium released in response to the action potential allows the heads of the myosin molecules to bind to actin, pulling the actin and myosin filaments past each other so that the myofibril contracts and the heart muscle 'beats'.

ICCs are caused by mutations in the components of the electrical and contractile system of the heart or its vasculature. Many ICCs interfere with the synchronised generation of the action potential or contraction of the myofibrils, causing characteristic changes in the electrocardiogram (ECG) and disturbance of the heart rhythm, or arrhythmia. Arrhythmias (which can also result from structural damage to the heart caused, for example, by ischaemia) may lead to symptoms such as palpitations, dizziness, chest pain, breathlessness, loss of consciousness or fainting and in the most severe cases may lead to cardiac arrest, or sudden cardiac death.

There are four main categories of ICCs (a more detailed description of the conditions is given in Appendix 1):

- arrhythmia syndromes caused by mutations in the proteins involved in generating the action potential; these are mainly the proteins making up sodium-, potassium- or calcium-conducting channels in the membranes of the cardiac myocytes, but also some proteins that affect ion conduction indirectly. The arrhythmia syndromes include conditions such as LQT syndrome, short-QT syndrome (Morita 2008), Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT).

- cardiomyopathies, caused mainly by mutations in the proteins making up the contractile system of the myofibrils, such as actin, myosin and troponin. The cardiomyopathies include HCM characterised by asymmetrical thickening of the heart muscle thereby obstructing the emptying of blood from the heart (Elliott 2008), and dilated cardiomyopathy (DCM), which weakens the

heart muscle. These conditions can lead to heart failure, stroke and arrhythmic defects in heart function.

- inherited arteriopathies, which cause catastrophic rupture of the blood vessels in addition to affecting other organs. These conditions include Marfan syndrome, caused by mutations in the protein fibrillin-1 (a component of connective tissue) (Dean 2007), Ehlers-Danlos syndrome and Loeys-Dietz syndrome.

- muscular dystrophies, a group of multi-system genetic disorders that cause progressive muscle weakness and death of muscle cells. Some muscular dystrophies affect the heart, leading to arrhythmias. Examples include Emery-Dreifuss muscular dystrophy and myotonic dystrophy.

In addition, and also included within the scope of this report, is the genetic disease familial hypercholesterolaemia (FH), which is caused by mutations in one of three genes involved in the uptake of cholesterol-rich low density lipoprotein into cells. This results in severe elevation of the blood levels of cholesterol and low density lipoprotein, leading to a high risk of premature coronary atherosclerosis (Austin 2004). The most common cause of FH is mutations in the LDL receptor (LDLR).

Many ICCs are characterised by high levels of genetic heterogeneity, which means that any one of many different mutations in a variety of different genes may cause the condition. For example, more than 400 different mutations in 12 different genes are now known to be associated with LQTS, which is classified into several different subtypes. More than 450 mutations in 13 genes encoding structural components of heart muscle are implicated in HCM, while more than 200 different mutations in the LDLR gene have been identified in UK patients with FH. Some ICCs show incomplete penetrance; that is, individuals who carry a disease-associated mutation may not always show clinical symptoms of the disease, or symptoms may be latent in the absence of triggering factors. Disease expression is also highly variable.

2.3 Epidemiology

An understanding of the epidemiology of ICCs is hampered by some of the individual conditions being uncommon (resulting in small numbers of cases, even in large populations), their high degree of genetic heterogeneity (making classification difficult), incomplete penetrance, and the difficulty of reliably distinguishing ICCs from common multifactorial conditions with similar symptoms. An additional problem is the fact that SCD is often the first clinical presentation. Establishing the cause of death can be difficult and some sudden deaths remain unexplained, even after extensive post-mortem examination. It is also important to realise that while sudden death is an important and dramatic complication of ICCs, other forms of morbidity and mortality (for example heart failure in cardiomyopathy and angina in FH) are also significant.

Over the age of 40, most sudden deaths are caused by coronary artery disease, whereas in younger people inherited causes are more likely. The proportion of deaths attributable to ICCs depends strongly on the definition used for this subset of SCD. There are varying criteria for the age range (for example, 4–64; or under 30, 35 or 40 years); timing of death (for example, within 1, 12 or 24 hours of presenting symptoms); and previous medical history (present or absent). The inconsistencies of these definitions make interpretation of published evidence difficult.

Unfortunately there are no national data to identify clearly the mortality, whether sudden or not, and morbidity due to ICCs. Two prospective studies based on coroners' reports have estimated the incidence (in England) of sudden deaths that are unexplained and may be due to arrhythmia syndromes. These are sudden deaths (often known as SADS, or sudden arrhythmic death syndromes) where the heart appears normal at post mortem examination. Bowker (2003) estimated 0.5 sudden unexplained deaths/ 100,000 / year in adult Caucasians aged 16–64, with an estimated 143 SADS deaths per year in England. Behr (2007) suggested that there was significant under-recording and mis-recording of SADS

deaths and estimated the rate as up to 1.34 deaths / 100,000 / year in Caucasians aged 4-64, and 544 annual deaths in England. Subsequent familial studies have suggested that up to half of these SADS deaths are explained by ICCs, especially LQT syndrome and Brugada syndrome and some subtle cardiomyopathies (Behr, 2003 and 2008).

While these studies included adult deaths up to the age of 64, the majority of SADS deaths tend to occur in the younger age groups. Neither of the studies included black or other ethnic minority groups. Nevertheless, these studies provide valuable data for estimating the order of magnitude of mortality due to SADS and hence some of the mortality caused by ICCs. The total mortality due to ICCs – which include conditions such as HCM or FH where pathological changes in the heart or its vasculature are evident on post-mortem investigation – is likely to be substantially higher.

We have carried out a literature search for estimates of the prevalence of the major ICCs, both worldwide and in the UK (see Table 2.1). Using these data, we have calculated estimated numbers of prevalent cases in the UK. Again, these estimates are fraught with caveats, particularly the difficulty of distinguishing accurately between ICCs and multifactorial disease. For some conditions (for example, arrhythmogenic right ventricular dysplasia) the ranges are very wide. It should be pointed out that Table 2.1 lists genetic conditions that affect only or mainly the heart. There are also other genetic conditions that have heart manifestations. Including these would increase the total prevalence.

Table 2.1 Reported prevalence of ICCs: International estimates, UK estimates, and estimated prevalent cases in the UK (for references see Appendix 1)

Condition	International prevalence	UK prevalence	Estimated prevalent UK cases (based on entire population mid 2007 60.98 million)
Hypertrophic cardiomyopathy	1 in 500 Europe		121,960
Familial Hypercholesterolaemia	1 in 500 Europe	1 in 500	121,960
Arrhythmogenic right ventricular dysplasia/ cardiomyopathy	1 in 1,000 to 1 in 10,000 European		6,098-60,980
Long QT syndrome	1 in 5,000 European	1 in 2,000 to 1 in 5,000	12,196-30,490
Dilated cardiomyopathy	36.5* in 100,000 USA		5,565*
Marfan syndrome	1 in 5,000 Worldwide	1 in 5,000	12,196
Brugada syndrome	146.2 in 100,000 Japan 1 in 5,000 European		12,196
Myotonic dystrophy	1 in 8,000 worldwide		7,623
Catecholaminergic polymorphic ventricular tachycardia	1 in 10,000 Europe		6,098
Ehlers-Danlos syndrome type IV	1 in 250,000 USA		244

Noonan syndrome	Birth prevalence 1 in 1,000 to 1 in 2,500 live births per year		Birth prevalence 267–669 per year (669,000 UK live births – 2006)
Barth syndrome	Birth prevalence 1 in 300,000 to 1 in 400,000 per year USA		Birth prevalence 152-203 per year
Dystrophinopathies		Birth prevalence 4 in 18,500 live male births	Birth prevalence 74 per year (342,000 UK live male births –2006)
Total (excluding FH)			**184,669-258,298**
Total (including FH)			**306,629-380,258**

* This estimate of prevalence for DCM is based on sparse literature and is thought to be an underestimate (Perry Elliott, personal communication). The figures shown are calculated on the assumption that approximately 25% of DCM is familial in nature.

The following conditions are not listed due to lack of identified prevalence data in the published literature: familial atrial fibrillation, short QT syndrome, progressive familial heart block, Loeys-Dietz syndrome, thoracic aneurysms and aortic dissections, mitochondrial dilated cardiomyopathy and Emery-Dreifuss muscular dystrophy.

Despite these difficulties, it is clear from Table 2.1 that, collectively, ICCs represent potentially a substantial burden of disease in the UK population. HCM and FH alone, with fairly well established prevalences of 1 in 500, together account for about 130,000 prevalent cases in the UK. As many of these people may not have overt symptoms, the challenge for health services is to identify and treat those at highest risk of major cardiovascular incidents or death while avoiding unnecessary intervention where the risk is low. In the case of FH, it is thought that about 75–90% of at-risk individuals remain unaware of their risk. As the penetrance of FH is very high, intervention may be justified for a substantial proportion of these people since, with statin treatment, their risk could be reduced to near the average population risk for coronary heart disease. Similarly, for many other ICCs, surveillance or preventive measures are available to reduce the risk of disease.

2.4 Risks associated with ICCs

Risk estimation for ICCs is difficult because of the heterogeneity within each condition, the effects of treatment, and the variability of risk with factors such as age and sex. Risk assessment is a complex process requiring multiple clinical investigations and expert interpretation of genotype, symptoms and medical history.

The overall population based-risk of the LQTS with expressed phenotypic evidence of disease is low when receiving appropriate treatment most usually with beta-blockers. Evidence from the international LQT registry indicates an approximately 4% risk of mortality over 40 years *i.e.* 0.1% per year and this observation is further supported by their most recent data. Indicators of high relative risk of sudden death include a personal history of aborted SCD or syncope and QT prolongation >500ms; absolute risks of death in patients with previous cardiac arrest or syncope despite beta-blockade increase to approximately 3-4% per year (Zareba *et al*. 2003). Recent syncope (within the last 2 years) is a stronger predictor of aborted cardiac arrest/death than is a more remote history of syncope (Hobbs *et al*. 2006). Gender and age also play significant roles in influencing the clinical course of LQTS in that cardiac events tend to occur more frequently in children, with males having an increased risk

of events during preadolescence and females having higher event rates in adolescence and beyond (Locati *et al*. 1998). Although it is often assumed that sudden death of a sibling is a risk factor for death in LQTS patients there is little evidence to support this. With regard to asymptomatic patients even with the highest risk genotype, absolute risk of death is less than 1% per year (Priori 1993).

In HCM, risks also vary widely. A minority of patients (10–20%) are at significant risk of death or serious morbidity. Most have much lower risks: about 55% have no recognised risk factors (Maron 2002) and about 25% reach a normal lifespan with no or very mild symptoms, and no requirement for therapeutic intervention. Average mortality from HCM is thought to be about 0.3–1% per year but higher risks of 2–6% per year are associated with some subtypes of the condition (Wald 1999, Maron 2003). Important risk factors for SCD include a prior cardiac arrest, a family history of premature HCM-related SCD, unexplained syncope particularly in young patients, abnormal blood pressure during exercise, and extreme left ventricular wall thickness. For example, in the 10% of HCM patients with a left ventricular wall thickness greater than 30mm, SCD risk has been estimated as 2% per year (Spirito 2001). Disease onset and progression are highly variable. For example, some individuals may be asymptomatic in childhood and early adulthood but develop left ventricle hypertrophy later in adult life, suggesting that clinical surveillance is important for all HCM mutation carriers (Maron 2003).

Data from the Simon Broome Register of UK FH patients suggest that before the introduction of lipid-lowering statin therapy, FH was associated with a 100-fold mortality from coronary heart disease for females aged 20–39 compared to the general population, and a 50-fold mortality in males in this age group (Betteridge 1999). There was a 10-fold mortality from all causes. These mortality ratios correspond to an annual coronary mortality of 0.17% in young women with FH and 0.46% in young men. At older ages, the annual coronary mortality increases but the mortality ratio is very much lower because of the steep increase in coronary mortality in the general population.

About 75–90% of people with Marfan syndrome develop heart problems such as aortic rupture or dissection, or prolapse of the heart valves, often during childhood or early adulthood (van Karnebeek 2001, Ho 2005). If untreated, the condition may be fatal by the age of about 30 years but recent improvements in management have increased life expectancy and about 30–50% of patients now survive into their 70s. The severity of cardiovascular symptoms is the strongest predictor of mortality. In a study of UK Marfan patients, those with the greatest cardiovascular severity (33% of the total) had a mean cumulative survival of about 45 years, compared with 70 years for those with the best cardiovascular status (Gray 1998).

In the muscular dystrophies, the risk of sudden cardiac death is variable both between and among the different conditions. Approximately 65% of adults with type 1 myotonic dystrophy have an abnormal ECG and sudden cardiac death occurs in 10–30% of patients (Longman 2006). The highest risks are associated with more severe abnormalities of the ECG and atrial arrhythmias (Groh 2008).

2.5 Diagnosis and management of ICCs: integrating cardiology and genetics

The diagnosis of ICCs frequently presents a complex clinical problem involving a range of highly specialised medical professionals, equipment and resources (see Chapter 6). Cardiological investigation may involve an array 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 more common forms of heart disease.

2.5.1 The clinical utility of genetic testing

Genetic testing, where available, can offer clinical utility by confirming or refining a provisional diagnosis, helping to distinguish acquired from genetic disease, clarifying the mode of inheritance and, in some cases, contributing to the assessment of risk and the choice of treatment.

If a mutation that is known to be pathogenic is identified in the patient, other family members can be offered targeted testing for the same mutation. Those who carry the mutation can then be offered appropriate surveillance and/or treatment, while those who do not carry the mutation can be spared further investigation. This approach, known as cascade testing, is discussed further below.

Genetic findings are not always clear-cut, however. 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 clinical features 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.

2.5.2 Clinical management

Once a diagnosis is made, risk stratification is an important feature of the management of patients and families, who need advice on avoidance of severe cardiac events or SCD. In some cases, an increasing understanding of the relationship between genotype (the mutation causing the disease) and phenotype (the clinical manifestations) is enabling risk assessment and management to be fine-tuned for the individual patient.

Management measures for ICCs include advice on triggers to be avoided, such as exercise or certain types of drugs. Accurate diagnosis is vital here, as the nature of triggering events and the response to drug treatment can vary widely. Genetic testing can make an important contribution. For example, the LQT1 subset of LQTS 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 (Morita 2008).

Treatment of ICCs might include drugs such as beta blockers or calcium channel blockers, or the use of implantable cardioverter-defibrillators (ICDs). Genetic test results can be used to guide therapies; for example, patients with LQT1 respond well to beta blockers while those with LQT3 do not respond to this class of drugs (Sauer 2007). In a subset of patients with HCM, obstructive thickening of a part of the heart muscle called the interventricular septum may be treated by alcohol septal ablation or surgical myectomy. FH is very successfully managed in most patients by treatment with statin drugs. Any risks associated with treatment must be carefully weighed against the benefits. For example, over the course of a lifetime, ICDs are associated with significant morbidity and limitations in quality of life. It is important that their use in an individual patient is justified by the level of that patient's risk.

Some routine aspects of care may be delegated to district general cardiology services. Others require ongoing input from the specialist ICCs service. Coordination of care between specialities and services is essential.

2.5.3 Cascade testing in the extended family

If a first-degree relative of the index case is found to share the clinical features of the condition, or the causative mutation, that relative can be offered appropriate clinical investigation, and testing can in turn be offered to their first-degree relatives, thus 'cascading' the testing through the extended family. Cascade testing can be carried out using the clinical phenotype (for example, elevated lipid levels for FH, or echo for HCM) but because of overlap between affected and non-affected subjects these traits have a high level of diagnostic uncertainty. This difficulty does not arise if a mutation can be identified in the index case, although incomplete penetrance can still make clinical risk estimation difficult. The cascade approach has proved effective for FH where, in index cases with the strongest clinical suspicion, a causative mutation can be identified in about 80% of individuals. As well as enabling expensive therapy and monitoring to be targeted to affected family members, cascade testing also

enables those who have not inherited the family mutation to be reassured and spared further (often invasive) testing. Cascade testing for several ICCs has been shown to be feasible and acceptable in the UK and to be cost-effective for both FH and HCM (see Box 6.14). The legal and ethical issues associated with the cascade approach are discussed in Chapter 7.

Boxes 2.1 and 2.2 present case studies that illustrate the complexity of the clinical and genetic investigations that need to be undertaken in the diagnosis and management of ICCs, and some of the difficulties of interpretation that frequently arise. In one of these examples (Box 2.1), investigation of the family is prompted by the diagnosis of an ICC in a living family member, while in the other (Box 2.2), the index case is a victim of sudden unexplained death.

Box 2.1 Case study: diagnosis and management of HCM

A 45 year old man, A, was diagnosed with hypertrophic cardiomyopathy (HCM) following a routine medical which revealed an abnormal ECG. He had no symptoms and risk factor stratification was reassuring. There was no obvious evidence of heart disease elsewhere in the family but, with a number of relatives at risk, DNA analysis was instituted to help with cascade screening. A myosin heavy chain gene missense mutation that is known to be pathogenic was identified.

Of A's three teenage children, two were found not to have inherited the mutation and were discharged from follow up without need for clinical investigation. His youngest child, an 11 year old boy, carried the mutation and was found to have a borderline abnormal ECG and a normal echo. Annual follow up was instituted and he was successfully encouraged to develop interests in appropriate non-strenuous sports.

A's parents (in their 70s) did not initially feel a need for assessment for HCM themselves but worried about their other children and grandchildren. Following a consultation with the genetic counsellor, A's father was found to have the HCM mutation. Clinical assessment revealed asymptomatic HCM but with episodes of atrial fibrillation on monitoring, denoting a very high stroke risk; warfarin anticoagulation was started. Ultimately, cascade screening of the paternal family revealed four other relatives with previously undiagnosed HCM; one was known to have cardiac hypertrophy but this had been attributed to hypertension. Whilst three of the four were found to have low risk features, a cousin of A, who had noticed occasional exertional chest tightness and an episode of syncope, was found to have worrying features. He received an ICD for primary prevention of risk of sudden death.

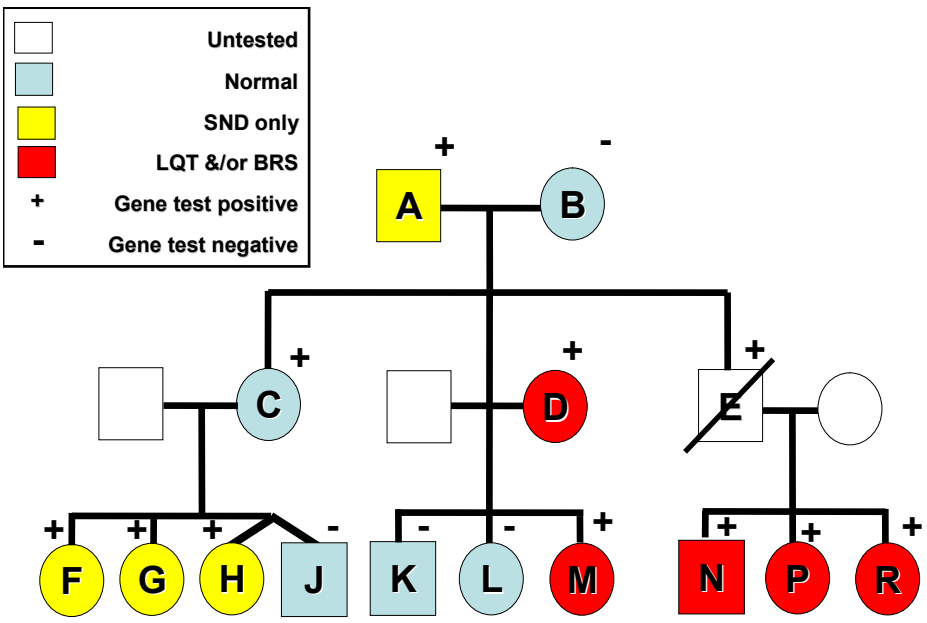
This (composite) family story illustrates several points:

- many individuals with HCM do not have symptoms or an obvious family history of the condition
- most will be found to be at low risk but some have significant risks (including, but not limited to, SCD) that can be reduced by interventions
- important lifestyle adjustments may be successfully achieved in younger children
- those who do not carry the familial mutation may be discharged, without the need for follow-up with repeated clinical tests
- cascade screening using phenotypic features is likely to be ineffective for HCM as diagnosis of the condition is more difficult in older patients (for example, because of hypertension) and in children or adolescents who have not yet developed obvious features.

Box 2.2 Case study: diagnosis and management of an arrhythmic syndrome

A 34 year old man (the individual labelled E in the pedigree shown below) who had no prior symptoms or medical history died suddenly while driving his car. Attempts at resuscitation failed and he underwent an autopsy at the request of the local coroner. The autopsy failed to identify a cause for the sudden death despite toxicological testing and evaluation of the heart by an expert cardiac pathologist. His asymptomatic children (N, P and R aged 5,7 and 8 respectively) underwent evaluation with ECG, 24 hour holter monitoring and echocardiography. All three demonstrated mild QT interval prolongation on their ECGs, with sinus node dysfunction (SND – abnormal slowing of the heart rate). In P and R, additional changes were observed that warranted ajmaline testing. These demonstrated features of the Brugada syndrome. Genetic testing of the LQTS genes in all three children revealed a mutation in the SCN5A gene. The same mutation was found in a small frozen tissue sample retained from E's autopsy. Mutations in SCN5A are responsible for the LQT3 variant of LQTS as well as the Brugada syndrome. The specific mutation found in this family is one of the most common found in LQT3 patients and in this family appeared to cause a combined condition. LQT3 is known not to respond well to beta-blockers, the mainstay of most LQTS therapy, so these drugs were avoided in the children. The children eventually had permanent pacemakers implanted to manage their LQTS and SND.

In the past E's older sister (D aged 42) had suffered a sudden blackout whilst walking, and when she was evaluated, had an ECG suggestive of the Brugada syndrome. She underwent ICD implantation as she was at high risk of sudden death. Her children (K, L and M) were asymptomatic. M's ECG was abnormal and subsequent genetic testing confirmed that D and M carried the family mutation. E's younger sister (C aged 32) had normal tests including a normal ajmaline test although genetic testing identified her, too, as a mutation carrier. Her children (F, G, H and J) underwent preliminary tests which only showed mild SND in F, G and H, who were later identified as mutation carriers. C, D and E's father (A) were tested, having had mild abnormality on his ECG, mainly suggestive of SND, and was shown to be a mutation carrier. B, J, K and L, all mutation-negative, were all excluded from any further follow-up or investigation and were reassured. All mutation carriers received appropriate preventative advice on lifestyle and medications to avoid.



This family demonstrates some important features of the evaluation of SADS and genetic testing:

- incomplete penetrance and variable expressivity: The signs and symptoms of ICCs such as LQTS and Brugada syndrome can vary dramatically in mutation carriers, from none to sudden death, and require expert evaluation to detect them and then instigate appropriate management.
- management of all mutation carriers: Even those mutation carriers who appear unaffected require long term follow-up to assess any change in their condition, especially as children become adults. They also require advice on lifestyle adjustments that could reduce the likelihood of cardiac events and sudden death.
- exclusion of mutation-negative family members: All blood-related mutation-negative individuals who might have required continuing follow-up without genetic testing could be excluded from follow-up.
- the molecular autopsy: Retention of frozen tissue or blood after a sudden death, especially in SADS, enables the pathogenicity of a mutation to be confirmed by testing for its presence in the victim's DNA.
- genotype guided therapy: Management can be guided, particularly in LQTS, by identification of the specific subtype of the syndrome.
- in some cases it may be possible to diagnose the cause of death by molecular autopsy prior to evaluation of the family. This is a potentially important role for the future.

2.6 Conclusions

ICCs are responsible for substantial mortality and morbidity in the population. In the population of the UK aged 4–64, it has been estimated that about 544 unexplained sudden deaths per year are due to genetic arrhythmia syndromes, which represent a subset of ICCs. The overall mortality due to ICCs is unknown, but prevalent cases of ICCs that increase the risk of SCD are likely to number in the hundreds of thousands.

Advances in cardiology, together with rapid progress in clinical and molecular genetics and a greater understanding of the natural history of ICCs, are revolutionising the diagnosis and management of these conditions. Effective treatments, surveillance or preventive measures are available for many ICCs, making it imperative that patients who could benefit from these interventions are recognised in the population. Risk stratification is essential in order to target treatments at those who are at the highest risk of SCD or other serious cardiac events.

Because of the complex and varied nature of the disorders, and the need to extend investigation to the families of affected individuals, it has become increasingly clear that effective services can only be provided by coordinated multidisciplinary teams of clinical specialists. The appropriate use of genetic testing, guided by expert knowledge and experience, will become increasingly important in the diagnosis and management of families.

Chapter 3 The policy context

The rapid scientific and clinical advances described in Chapter 2 have provided the impetus for clinical policy developments to address the needs of patients and families affected by ICCs. These developments have included policy initiatives within the NHS, and initiatives by professional groups such as pathologists, coroners and specialist cardiologists, and charitable foundations including the British Heart Foundation (BHF), HEART UK, STARS (the Syncope Trust And Reflex anoxic Seizures), the SADS (Sudden Arrhythmia Death Syndromes) Foundation, CRY (Cardiac Risk in the Young), CMA (the Cardiomyopathy Association) and the Arrhythmia Alliance.

At the commissioning level, there are moves towards a formal recognition of ICC services as specialised services operating within regional cardiac networks.

A number of the policy initiatives described in this chapter (for example, the National Service Frameworks and organisational structures such as the cardiac networks) are specific to England and Wales. Other developments such as BHF funded posts are UK wide. Although we focus primarily on developments in England, parallel initiatives in the devolved nations are noted where possible.

3.1 The National Service Framework for Coronary Heart Disease

The National Service Framework (NSF) for Coronary Heart Disease, published in March 2000, set out a framework for provision of improved services for the prevention, diagnosis and treatment of coronary artery disease but did not specifically mention ICCs. Early in 2004, a high-profile Private Member's Bill seeking effective and automatic NHS screening for all families at risk of SCD was presented to Parliament. The bill, named 'Cardiac Risk in The Young (Screening)', proposed by Stockton South MP Dari Taylor and instigated by CRY, received extensive media attention and strong support from other charities and a number of well-known sportsmen (such as Ian Botham and Jeremy Bates). In response, in March 2004 the Department of Health published a consultation paper for a new chapter for the NSF concerning cardiac arrhythmias and SCD. An expert group, chaired by Dr Roger Boyle, was established to consider the views received and draft the new chapter within 12 months. The consultation paper specifically highlighted the impact of Dari Taylor's bill in raising important issues for consideration in the new chapter (Chapter 8), which was published in March 2005.

The requirements in Chapter 8 of the NSF concentrate mainly on the needs of patients with acquired (multifactorial) arrhythmias. Issues of family risk are included in the quality requirement related to SCD, which requires systems to '*identify family members at risk and provide personally tailored, sensitive and expert support, diagnosis, treatment, information and advice to close relatives*'. With respect to SCD the chapter comments on the importance of:

- good awareness in primary care
- the role of the coroner in determining the cause of death and the opportunity to assess potential risk to the family
- effective evaluation of relatives, guided by genetic testing.

The guidance recommends that evaluation of families should take place in a dedicated clinic with staff who are trained in diagnosis, management and support and with genetic counselling and further testing available if appropriate.

Initial lack of progress in implementing the recommendations of Chapter 8 of the NSF can be attributed to a number of factors, including a lack of clarity on: the scope of service provision (should the focus be on sudden cardiac death alone or on all ICCs?); whether all local cardiac networks should be developing their own centres of excellence or working with other networks; the number of centres of excellence needed to ensure access to a high quality and cost-effective service; the service model and its specification; and how the service should be commissioned.

During 2006 two unpublished surveys of current service provision, carried out on behalf of an informal cardiac genetics group and the Heart Improvement Programme (HIP), showed that whilst some comprehensive services existed, provision was patchy, and there were considerable variations in referrals to services and in the use of clinical and genetic testing guidelines (Brennan 2006, Heart Improvement Programme unpublished survey). These surveys also highlighted the importance of other ICCs not originally included in Chapter 8 of the NSF, such as certain cardiomyopathies and Marfan syndrome, which also require expert cardiac genetics input. These findings have emphasised the need for services to have a broader remit than originally specified in the NSF.

New guidance for implementing Chapter 8 was published in March 2007, when Dr Roger Boyle, National Director for Heart Disease and Stroke, wrote to all cardiac network leads. This document subtly shifted the scope of services to include also '*the investigation of risk and treatment of inherited cardiovascular diseases*', as well as the original requirement for dealing with SCD. This change in emphasis is also reflected in the title of the National Sudden Cardiac Death and Inherited Cardiac Conditions Delivery Group; again, broadening the scope of implementation to include other inherited cardiac conditions.

3.2 Policy initiatives in Wales, Scotland and Northern Ireland

The NSF for coronary heart disease applies to England and Wales. In Wales, the NSF was adopted in 2001 and cardiac networks were set up in 2002. In September 2008 the name of the NSF was changed and an 'Interim Cardiac Disease NSF' was published that included an additional standard (standard 5) on arrhythmias and inherited cardiac disease (Welsh Assembly Government 2008). A full Cardiac Disease NSF that includes a further standard on adult congenital heart disease has been developed and is under consideration by the Welsh Assembly Government.

In Scotland, a national advisory committee for coronary heart disease was set up to provide policy advice and to facilitate strategic planning following the publication of the National Strategy for Coronary Heart Disease and Stroke in October 2002 (Scottish Government 2002). In July 2008 a consultation document entitled *Better Coronary Heart Disease and Stroke Care* was published (Scottish Government 2008). One of the three areas it highlighted for increased prominence was ICCs including those resulting in SCD. One mechanism for addressing ICC services has been the development of the Familial Arrhythmia Network Scotland (FANS) which is aimed at raising awareness of familial arrhythmias, developing referral protocols and national guidelines for clinical and genetic testing and establishing a national register. The register will support long term follow-up, including testing for the late onset of a condition, administration of new therapies and scope for identifying new genes and genetic tests as they become available. A parallel network for cardiomyopathies is planned. Links will be made to the existing Scottish Muscle Network, which covers cardiac problems related to inherited neuromuscular conditions such as myotonic dystrophy or Duchenne Muscular Dystrophy. It is expected that these Networks will be merged into a fully multidisciplinary specialist Network covering all inherited cardiac conditions.

In Northern Ireland there has been no overarching policy framework. Services are planned by each of the four health boards and social services boards but an amalgamation of the four boards into a single Regional Health and Social Care Board is planned for April 2009. This situation will further change as in 2008, a service framework for cardiovascular health and wellbeing was circulated for consultation (Northern Ireland Government 2008). Within the framework there is a standard on inherited cardiac conditions which will be finalised in 2009.

3.3 The 'blueprint' document

In 2007 the DH endorsed a document entitled *Proposal for the Establishment of Inherited Cardiovascular Conditions Centres*, produced by Prof William McKenna of the Heart Hospital (London) and an unattributed informal advisory group (McKenna 2007). The guidance anticipated that around

10 centres of excellence might be designated in England. It makes recommendations on staffing requirement, equipment requirements, information sources for patients and about '*coordination with electrophysiological services, interventional cardiology, cardiothoracic surgery and cardiovascular imaging*'. Described as a 'blueprint' for services and quoted many times in DH meetings, the document makes a strong case for a more concerted approach to ICC services. However, it is not comprehensive in its consideration of an ICC service (being focussed mainly on SCD) and would benefit from inclusion of clear and measurable standards and also more extensive consultation with all the appropriate stakeholders.

3.4 Other policy initiatives

3.4.1 UK Cardiac Pathology Network and Special Interest Group

Given the importance of pathologists in the investigation of SCD, in late 2006 the Royal College of Pathologists endorsed the establishment of a national network of pathologists for improving the standard of the cardiac post mortem in diagnosing the causes of SCD. The UK Cardiac Pathology Network (UK-CPN) now has over 40 members. The aims of the organisation are to develop a network of pathologists throughout England and Wales to provide coroners with an expert cardiac pathology service locally and nationally and to promote best pathological practice in sudden death cases, including provision of protocols for pathologists based on Royal College guidance. The Network's Steering Group includes representatives of general and forensic pathologists, the Coroners' Society and the Coroner's Officers Association as well as expert cardiologists and cardiac pathologists. A key element of the network is the development of a national database for young sudden death victims that will provide epidemiological data on the frequency of SCD, as well as important demographic information.

The DH has also created a National Coroners and Pathologists Special Interest Group to provide guidance to both coroners and pathologists dealing with SCD. Again, charities such as CRY have been actively involved in lobbying for such improvements and the need for access to high-quality, expert cardiac pathologists in SCD syndromes. CRY currently funds an expert cardiac pathologist to provide this service to families.

3.4.2 British Heart Foundation initiatives

The BHF is developing a UK-wide Genetic Information Service (GIS) planned to be operational from April 2009. Where an ICC is suspected, coroners will be asked to give first-degree relatives of the deceased person the contact details for the GIS, which will then provide relatives with

- contact details for patient organisations that can provide information and support
- a letter for them to take to their GP recommending referral to an ICC service that is appropriate to the family's needs, both clinically and geographically. The BHF's list of services to be used by the GIS has been compiled from information provided by the cardiac networks and from the survey carried out as part of our service review.

This initiative has had the benefit of bringing together a large number of stakeholders working in this field and provided another forum for discussion of key issues in improving services for ICCs and SCD.

The BHF has made funding available for Trusts offering ICC services to apply to appoint a Cardiac Genetic Nurse. Two posts were funded in Belfast and Leeds in 2006; the success of this initiative and the increased demand for ICC services led to the BHF providing funding for an additional 9 posts (University of Oxford, Oxford Radcliffe Hospital; University College Hospitals NHS Secondary Care Trust; University Hospital Birmingham; City Hospitals Sunderland NHS Foundation Trust; Nottingham University Hospital; Cardiff and Vale NHS Trust; King's College and Guy's and St Thomas's; Cambridge University NHS Trust with Papworth Hospital NHS Foundation Trust; St George's Healthcare Trust). Funding is for a three-year period, after which the Trust is expected to fund the post in the longer

term, with continuing support from the BHF nurse adoption programme. The role of the Cardiac Genetics Nurses is to improve access to ICC services for patients and their families, offer support and education, and assist the coordination between cardiac and genetics services.

3.4.3 Heart Rhythm UK position statement regarding clinical indications for genetic testing in familial sudden cardiac death

Heart Rhythm UK is an affiliated group of the British Cardiovascular Society, bringing together professionals involved in arrhythmia care in the UK. A position statement, first published on-line in late 2007, has provided an excellent summary of the role of, and indications for, genetic testing in SCD (Garratt 2007). Further work by members of Heart Rhythm UK is being undertaken on guidelines for the use of ICDs in people at risk of SCD. This is very important, as these devices are very expensive and need to be used in a cost-effective way.

3.5 Familial hypercholesterolaemia

Funding to pilot cascade testing for FH in England was announced in June 2003 in the Government White Paper on genetics in the NHS: *Our Inheritance, Our Future* (Department of Health 2003). The project was managed by a coordinating team based at UCL within the London IDEAS Genetics Knowledge Park. Five sites covering 11 lipid clinics were funded with a full-time nurse for 2 years. A report of the project was presented to the Department of Health in October 2007 (Familial Hypercholesterolaemia Cascade Testing Audit Programme 2007) and is available at www.fhcascade.org.uk. The report concluded that cascade testing using specially trained nurses integrated in lipid clinics (a secondary referral outpatient setting) is feasible and is acceptable to patients and clinicians. Recommendations for effective implementation included the development of a national integrated infrastructure for the service; the use of DNA testing rather than phenotypic (cholesterol) measurements; the development of specialist services for the management of young people with FH; and education for primary care teams to ensure that patients with FH are identified and offered appropriate care.

In August 2008, the National Institute for Health and Clinical Excellence (NICE) published a clinical guideline containing 109 recommendations on the identification and management of people with FH (National Institute for Health and Clinical Excellence 2008). One key recommendation is that DNA tests should be offered to all those with a clinical diagnosis of FH and that cascade screening be systematically implemented in families affected by FH, including '*the use of a nation-wide, family-based follow-up system … to enable comprehensive identification of people affected by FH*'. This is the first UK clinical guideline to recommend a systematic cascade testing programme for a genetic condition. Testing will include a combination of genetic testing (where the mutation is known) and measurement of LDL concentration, to identify affected first-, second- and (if possible) third-degree relatives of a person with a clinical diagnosis of FH. The guidance also states that the possibility of FH should be considered in anyone with raised LDL cholesterol, especially where there is a family history of premature coronary heart disease. In children at risk of FH because of an affected parent, diagnostic tests should be carried out by the age of 10 years.

3.6 Chronology of main policy initiatives for improving inherited cardiovascular conditions services in England and Wales

March 2000	Publication of the National Service Framework for Coronary Heart Disease
June 2003	White paper on Genetics and the NHS (*Our Inheritance Our Future*) includes the FH cascade audit project
March 2004	Dari Taylor's Private Members Bill "Cardiac Risk in the Young (Screening)"
March 2004	Consultation paper published for new NSF chapter on arrhythmias and sudden cardiac death
March 2005	Publication of chapter 8 of the NSF
May 2006	Survey of Cardiac Genetics Services in the UK by Dr Paul Brennan on behalf of an informal cardiac genetics group
September 2006	Foundation for Genomics and Population Health invited to conduct a comprehensive review and needs assessment
November 2006	Heart Improvement Programme survey of cardiac genetics services
March 2007	New guidance issued to cardiac network leads regarding implementation of chapter 8 of the NSF
	Heart Hospital "blueprint" document endorsed
	Launch of fast track cardiac pathology service instigated and funded by CRY
During 2007	UK Cardiac Pathology Network, and Coroners and Pathologists Special Interest Group, established
	Heart Rhythm UK publishes guidelines and indications for genetic testing in sudden cardiac death
October 2007	Report on FH cascade audit project received by Department of Health
February 2008	HEART UK publish results of survey of UK lipid clinics (see Chapter 5 for further description)
August 2008	NICE publishes clinical guideline on familial hypercholesterolaemia
November 2008	Establishment of Central Cardiac Audit Database and SADS database
April 2009	Launch of BHF Genetic Information Service
	Report of DH-funded pilot audit of FH services in the UK

3.7 The commissioning of ICC services in England

Commissioning of cardiology services needs to encompass a number of levels depending on the expected volume of service. PCTs or groups of PCTs are responsible for the bulk of cardiology services provided to a local population.

Within the NHS, some services are formally designated as specialised, meaning that they require a supra Strategic Health Authority perspective to ensure that the strategic planning of these services takes into account the appropriate population base. These are low volume, discrete services that need to be undertaken within specialist centres or be supervised by a specialist centre to ensure that there is sufficient volume of activity taking place to maintain skills and to offer an environment that enables clinical, technical and research needs for these services to be addressed. Although some activity might take place outside the specialised service where appropriate expertise exists, it should be overseen by a specialist centre. Specialised commissioning groups (SCGs) include commissioners who are responsible for this agreed portfolio of services.

The definitions for the current set of specialised services are being reviewed by the national commissioning group. At present they do not include ICCs as a discrete group, although at a recent meeting (October 10th 2008) of the DH Chapter 8 team with commissioners and cardiac network managers it was agreed that inclusion would be helpful. Current definitions do however include clinical and laboratory genetic services, some specialised electrophysiology, the management of four rare inherited conditions that cause arrhythmias and also services for adult congenital heart disease.

Costing and pricing mechanisms are an important aspect of the commissioning process that can influence whether and how Trusts wish to develop specialised services. These are the mechanisms by which Trusts are reimbursed for outpatient visits or inpatient stays. Under current policy they are nationally derived, dependent on the Healthcare Resource Groups (HRGs) into which the conditions or procedures are assigned. (HRGs are assigned by the NHS Information Centre with help from expert working groups and are meant to group together conditions and procedures that are expected to use similar amounts of healthcare resources). This has often meant that services providing complex healthcare – such as ICC services in which multiple specialists need to contribute and specialist investigations need to be undertaken – tend to lose out. Mechanisms do exist for 'specialist top-up' for some procedures, which can help highly specialised centres providing expensive and complex procedures. This may be facilitated for an individual hospital by being a designated provider for a particular service.

3.8 Cardiac networks

Under the Heart Improvement Programme, established in 2000 as part of NHS Improvement, cardiac networks have been established in England. By 2005, the bulk of the national resource held by the Coronary Heart Disease Collaborative had been devolved to these regional networks.

The cardiac network's prime role is to improve services by considering the overall picture of patients' journeys through the healthcare system, across primary, secondary and tertiary care. In doing so the network provides advice to commissioners and brings them together with clinical teams, patients and other stakeholders working across organisational and professional boundaries. The aim is to develop effective care pathways (including referral criteria and treatment protocols), raising the quality of clinical care and improving patient experience.

For specialist services, cardiac networks work with commissioners to agree what will be provided by the network itself (this might be for the local population or a wider population) and, for any services not provided by the network, what arrangements will be needed to ensure that patients are referred to appropriate other specialist services. The network is responsible with commissioners for ensuring that any specialist services provided by the network meet agreed professional standards. As discussed in Chapter 6, some of the current services for ICCs operate formally within the cardiac network.

3.9 Conclusions

Together, the policy initiatives described convey the impression of an integrated service developing to meet new clinical requirements. There has been increasing recognition of ICCs within NHS policy, and professionals and charitable foundations have had considerable success in influencing and working with the NHS to develop policy for these conditions. These developments are certainly to be welcomed.

The experience of patients and health professionals in this field, however, is that there is much still to be done to establish ICC specialised services on a secure and effective footing. Until recently the policy agenda, particularly at the political level, has tended to focus on the arrhythmia syndromes and has lacked an overall strategy to address the full range of ICC services. Coordination across the whole of the UK, which will be essential for the implementation of cascade testing programmes, is lacking. There is a perception of a shortfall in capacity and a fragmented approach to the implementation of multidisciplinary clinical care, with large regional variations in the service offered to patients. One aim of this review was to provide an objective assessment of current services, explore both examples of good practice and gaps in provision and, where possible, make recommendations for improving and developing services.

Chapter 4 The patients' perspective

4.1 Introduction

Patients' views on cardiac genetic services were sought through a focus group meeting to which representatives of the voluntary sector patient support groups were invited. The meeting, held on 9 September 2008, was attended by representatives from Cardiac Risk in the Young (CRY), Cardio and Vascular Coalition, Cardiomyopathy Association (CMA), Contact a family, the Down's Heart Group, the Genetic Interest Group (GIG), HEART UK, the Marfan Association UK and SADS UK. This chapter is their report.

4.2 Features of a good service

Participants were asked to discuss the features that would characterise a high quality inherited cardiovascular conditions service, and to rank these in order of importance. The clear message that emerged from the discussion was the need for:

- timely referral to services, with minimal waiting times
- recognition that the whole family requires care, not just individual patients
- a 'one-stop shop' for diagnosis and management of ICCs, with effective communication and coordination among specialist clinicians and with other supporting services
- increased capacity within ICC services, to ensure that care is received by all those who require it.

Marfan syndrome: one family's experience

I am 27 years old, with two little girls aged 5 and nearly 3. My older daughter has been diagnosed as a Marfan sufferer. She was originally thought to have cerebral palsy, to a very minor degree, but that was before my husband was diagnosed as having Marfan syndrome. Once it was realised that he had Marfan, tests showed that our older daughter had inherited the condition. Luckily our younger daughter is unaffected.

Unfortunately my husband was not diagnosed until his aorta had torn away from his heart. Although he had several major operations in an attempt to save him, he lost his battle to live through an infection in the new graft they put in. He died only one month after our younger daughter was born.

Looking back, and with the knowledge I now have about the condition, I realise he was an obvious case with his height of 6 feet 11 inches, indented chest, very flexible joints etc. If he had been diagnosed earlier in his life, and had received appropriate monitoring and treatment, I am sure he would still be alive today.

4.2.1 An effective pathway to diagnosis for the affected individual and their family

The highest priority was assigned to the need for a service that recognises, from the earliest stage, the familial nature of ICCs, especially where there is a sudden death of a young person, and provides timely access to specialists who are expert in the diagnosis and management of these conditions.

> "*The person at the start of the chain, whether it is the GP or in the event of a death, the coroner or the initial person dealing with the patient in hospital, needs to recognise the possibility of familial consequences, otherwise the chain breaks at the first link.*"

There should be a framework for action and clear, disseminated guidelines to ensure that coroners, GPs and local cardiologists recognise 'red flags' that suggest a sudden unexplained death may be the result of an ICC, and act swiftly to refer the case to a specialist – in most cases, a specialist cardiologist – who can make an accurate diagnosis of the condition and initiate referral of the immediate family of the index case for counselling and investigation. There should be a minimised but realistic timescale for the referral process; in cases of very high risk to the family, referral should be expedited as much as possible. At present the system works reasonably well where there has been a sudden death of a young person under the age of about 25, partly because parents are usually still closely involved with their children up to that age, and partly because paediatric cardiologists tend to be more aware of genetic conditions than their colleagues who work with adult patients. In addition, the voluntary groups are proactive in raising awareness among GPs and coroners. However, where the death is of a young person between 25 and 40, it is much less likely to be recognised as indicating an ICC, especially if the death does not occur in hospital.

4.2.2 Holistic and integrated care: an effective 'one-stop shop'

Once referral to the specialist service has taken place, whether in the case of sudden death or where the index case is still alive, there needs to be effective liaison between cardiologists and geneticists, to ensure that appropriate tests (which may or may not include genetic tests) are offered, and that the first degree relatives of the affected person have access to genetic counselling so that they understand their risk and the options available to them. At present, liaison is less effective than it could be. For example, familial hypercholesterolaemia has traditionally been managed by lipid specialists, with little involvement of genetics. Conversely, for some conditions that have been traditionally managed within specialist genetics centres (such the muscular dystrophies), there may have been inadequate recognition of heart involvement in the condition.

Those affected by ICCs, and their families, need an integrated, multidiscliplinary service. Diagnosis of an ICC should trigger a holistic approach to treatment and support, involving not just the physical aspects of the condition but also the psychological and social aspects.

Many ICCs, especially multi-system conditions such as Marfan syndrome, require the involvement of several different specialists. Ideally, clinics should be coordinated so that patients do not have to make many separate hospital visits to see different consultants. Care is more coherent if one specialty has central responsibility for care, but the identity of this specialty will be different for different conditions. There should also be a smooth process for consultant-to-consultant referral, so that patients do not have to go back through their GP, although it is vital that GPs are kept informed.

> "*Assuming you are able to access the service and you are referred to a cardiologist, the odds are that the cardiologist will be specialising in something you don't have, so there needs to be a good mechanism for consultant to consultant referral, always keeping the GP in the loop, that does not require patients and families to bounce back to their GP unnecessarily, wasting time and energy. There are administrative and organisational barriers that do not necessarily reflect the clinical needs of the patient.*"

For conditions where some aspects of care can be managed effectively through local cardiology services, there needs to be a clear division of responsibility, and adequate communication between the local and specialist services.

> "*There is often a block between the general cardiac service and referral to a more specialist service – there isn't a clearly defined flag that indicates when a person should be referred.*"

Patients often experience a fragmented pattern of care, with a lack of continuity. If possible, patients should see the same specialist at each appointment. Continuity could also be improved if patients had a single, named point of contact or care manager within the specialist service, to coordinate care and

liaise between specialists on the patient's behalf. This role could perhaps be carried out by a specialist nurse. (This is, effectively, the model that is currently being trialled in some centres by BHF-funded specialist nurses.) A single point of contact for patients was considered to be particularly important not only for the patient but also for other family members to initiate access to services.

The care manager or coordinator could also be responsible for ensuring that patients are aware of and helped to contact the patient support groups for people with their condition, and are directed to sources of accurate information.

An effective ICCS would have mechanisms for ensuring a smooth transition from paediatric to adult services – often a weak point for genetic conditions.

> "*The transfer from paediatric to adult services is often a point where people drop through the net…. Often there is not an equivalent service and patients in that age group often go into denial about their condition.*"

4.2.3 Access to genetic testing

Genetic testing, where appropriate, should be available in a timely manner. There should be geographical equity in access, and adequate funding and capacity for testing. Specialist cardiologists should be aware of the role of genetic testing in management of the patient and assessment of risk in other family members.

> "*There needs to be a good strategy for managing the results of the tests. Getting the results of the test in itself is not sufficient as sympathetic explanations and support are required, firstly from the Specialist together with ongoing support from the GP and the relevant patient support groups. One has to accept that some patients may feel distraught, and even suicidal after receiving the results of tests. Therefore close collaboration is particularly essential for all involved with the patient at this stressful time, especially encouraging the patient to continue with all necessary hospital appointments and prescriptions.*"

4.2.4 Patient empowerment

Patients within an effective ICCS should be empowered to make informed choices about the management of their condition or risk, and in particular to ensure that they are appropriately referred to specialist services, especially genetics services. This is particularly important for social or ethnic groups that are disadvantaged or under-represented in current services. However, complex social, cultural and religious beliefs may be involved in patients' attitude to their condition, and it is important that these are respected.

4.3 Gaps in current service provision

4.3.1 Genetics

Frequently there is a lack of referral to genetic services, usually due to inadequate collaboration between the specialist services. Patients often do not receive adequate information about the genetic aspects of their condition.

> "*Genetic conditions are a problem unless you are very lucky. Outside a big city centre, you don't have genetic services. The only person who is going to take up your case is the cardiologist and the cardiologist may not have an interest in genetics.*"

Patients have difficulty in accessing genetic testing, which in some cases could help achieve a more accurate diagnosis of their condition and its associated risks. The patient group representatives pointed

out that a genetic diagnosis of a condition has the potential to save the health service money, because family members who do not carry the familial mutation can be spared medical surveillance.

Timescales for genetic testing have in the past been unsatisfactory, with patients and their families sometimes waiting a year or more. National standards now require a maximum of 8 weeks for reporting of genetic test results. These standards are to be welcomed but are only effective if the need for testing has been recognised and the test initiated in a timely manner.

> "*There is a need for a timescale for achieving a diagnosis which reflects the implications of the condition. If you have a child who sadly loses his or her life from the condition and there are other children at risk you don't want to have to spend 12 months trying to get a diagnosis. The timescale needs to reflect the implications of the condition to other family members.*"

Systems for re-contacting patients in the future, perhaps when new tests have become available, are not always in place. Patients should also be able to initiate re-contact at times in their lives when they need further genetic advice; for example, if they are planning to start a family.

> "*Sometimes it is years on before something is found in a family – a system needs to be in place to contact the family and assess the current family situation.*"

4.3.2 Standards of care

There are currently too few specialists and specialist teams, which should include not just cardiologists and geneticists, but, depending on the condition, a wide range of professional expertise such as specialist nursing, dietetics and pain management.

Although clinical standards and pathways of care have been developed for some conditions they have not always been implemented, particularly for the rarer conditions. This can lead to patchy provision of care.

Patients are often coping simultaneously with both the loss of a young family member and the news that they may also be at risk. Counselling services, including bereavement counselling appropriate to the patient's age and needs, are not adequate at present.

There is a lack of effective feedback to patients' GPs about their condition; as a result, GPs are often not able to offer effective support.

4.3.3 Structural and commissioning issues

A lack of commissioning standards means that services are very variable across the UK. There is a need to develop more productive and constructive relationships between policy makers/DH, commissioners, providers, and the voluntary groups that represent patients.

> "*There is an absence of commissioning standards – people don't know what to pay for.*"

A lack of 'joined-up budgets' is hampering effective cascade testing within families. For example, GPs may be reluctant to refer family members who are concerned about their risk, because of the impact on the PCT budget.

4.3.4 Support for voluntary groups

The patient group representatives felt that there is currently insufficient recognition of the role voluntary groups play in supporting patients, and insufficient support for their work. Some grants are available but there is an emphasis on novelty rather than sustained investment.

4.4 The patient pathway

The focus group participants were asked to consider the routes through which patients access specialist inherited cardiovascular conditions services. The internet was seen as an important source of information but there was concern that patients may not always be able to find high-quality information. Research into the search strategies people use if they suspect they or a family member have a genetic cardiac condition would be very helpful. NHS Direct, or other NHS websites such as the National Library for Health which has a specialist library for genetic conditions, should be well-equipped to provide information not just about the conditions themselves, but about how people can access appropriate services. Patient groups and other voluntary organisations also provide much information in both web-based and printed format. Any validation or kitemarking to assure the quality of patient information should be carefully undertaken in close collaboration with patient support groups, which have a good awareness of patients' needs and an understanding of the terminology concerning their specific conditions.

There is often a block between general cardiac services and referral to the specialist services required by those with ICCs, particularly for conditions that may be difficult to distinguish from more common, multifactorial cardiac conditions.

> "*If you are going to have a specialist centre you need to agree what are the facets that make up a specialist centre. There needs to be clarity about which aspects of the condition can and ought to be dealt with locally and which aspects ought only to be dealt with by those people with a certain level of expertise.*"

There is a need for guidelines to flag up the indications for referral. Some voluntary groups are taking a proactive approach to educating health professionals about ICCs, for example by taking out advertisements in professional journals.

Once referral has occurred, the care pathway may involve specialist services, local cardiac services and the patient's GP. This only works effectively when there is close liaison and coordination among the different parts of the service.

4.5 Cascade testing

Strategies for managing a number of genetic conditions include cascade testing in the extended families of affected individuals. There are many obstacles to effective cascade testing, including clinical issues, psychosocial barriers, family disputes or estrangement, financial obstacles and legal constraints. In reality, cascade testing is rarely at present being extended to blood relatives beyond the immediate family.

The participants were asked to consider the best approaches for initiating cascade testing within a family. Normal practice within genetics services is for the genetic counsellor to suggest that the patient makes the initial approach to other family members who may be at risk. If the patient prefers, the counsellor or clinical geneticist may initiate contact on their behalf. In the pilot of cascade testing for FH, described in Chapter 3, specialist nurses in the lipid clinics managed the process of drawing up family trees and identifying and contacting relatives, generally initiating contact through the index case.

There was agreement that, when cascade testing is appropriate, the process of contacting relatives has to begin with the index case because permission is required to disclose their confidential information. Patients should be asked whether they wish to contact relatives themselves, or would prefer their consultant or GP to contact relatives by letter.

Geographic dispersal of families can make cascade testing difficult. An effective system depends on a service being available where the different family members live. A national network of specialist centres would facilitate access. The problem is exacerbated by the separate organisation and funding of healthcare in England and the devolved administrations in Wales, Scotland and Northern Ireland. Family testing information must be organised so that it can be easily transferred across such artificial funding boundaries, to ensure equality of access. People wishing to access services may face financial problems, either due to the need to travel long distances to a specialist centre or because local commissioners are unwilling to fund testing.

Participants pointed out that difficulties may arise if the index case is unwilling to inform relatives about their risk. There are also data-protection issues involved in sharing information about extended families among health professionals in different centres. These questions are discussed further in Chapter 7, which covers ethical and legal issues associated with ICCs and their management. Patient organisations, such as the Marfan Association UK, felt that the index case should be made fully aware of the risks that their family members may be facing.

4.6 Conclusions

The patient group representatives agreed that the two most important attributes of an effective ICC service were timeliness and the provision of an effective 'one-stop shop' that provides integrated and holistic care for patients and their families.

A major problem at present is lack of awareness of ICCs among coroners, non-specialist cardiologists and GPs, leading to delays in referral of patients and/or their families to specialist services. Development of guidelines, and the education and training of coroners and health professionals, are essential.

Within specialist services, cardiologists do not always refer patients appropriately to genetics services, with the result that patients may not be offered appropriate genetic tests or receive adequate information about the genetic aspects of the condition. Again, evidence-based guidelines and care pathways should be developed to highlight the specialist services required for different conditions.

Investment is needed in providing a holistic, integrated service for the care of those affected by, or at risk of, ICCs. The service should provide continuity of care, including re-contact at different stages of life when further advice may be needed, or when research developments have led to new interventions becoming available. The group recommended that patients should have a single, named, health professional (such as a specialist nurse) to be their main point of contact with the service and to liaise between local and specialist services.

There should be improved recognition of, and support for, the role that voluntary organisations play in supporting and informing patients about their condition, and in raising awareness among GPs and other non-specialist health professionals.

Chapter 5 Comparative survey of ICC services

5.1 Introduction

The purpose of the survey was to identify the main providers of specialist ICC services in the UK and to obtain information on the services offered, the staffing levels and numbers of clinics, the number of patients seen, the genetic testing associated with the clinics and the shortfalls in services. As well as providing a general description of the services that exist in each of the main Strategic Health Authority (SHA) areas of the UK, and in Wales, Scotland and Northern Ireland, this chapter also provides quantitative comparisons of the overall service provision and some estimates of activity in relation to relevant populations. The more qualitative aspects of services are discussed in Chapter 6: 'What makes a specialist service?'

5.2 Method

Information was collected by questionnaire to services. An initial questionnaire was sent to regional genetic centres in December 2007 asking them about the broad range of ICC services for arrhythmias, cardiomyopathies, Marfan syndrome, inherited congenital heart disease and familial hyperlipidaemia in their region and asking them to provide contact details for lead clinicians in each service. A detailed questionnaire was then sent to each ICC service identified. This took place between January and March 2008. Reminders were sent out to services in this period to ensure as full a response as possible. After initial analysis it became evident that questions may have been interpreted in different ways. Each service was therefore followed up individually during the summer of 2008 and asked to confirm or, if they wished, expand on information provided (particularly with respect to service overview) and to clarify detailed information on important quantitative aspects including number of outpatient sessions provided, professional clinical input and activity information. During Autumn 2008 a further letter was sent to each cardiac network manager providing the list of services identified and asking them to inform us whether any further services had been missed.

There were two versions of the follow-up questionnaire. One asked for information on Marfan clinics and had a number of questions that related specifically to Marfan services. The second questionnaire was relevant to the other ICC services (see appendix 2 for copies of the two questionnaires).

Comparative information about services was calculated in two ways. The first method used catchment populations given to us by the services. The total service for a given centre was calculated; service provision and activity for Marfan patients was added to that of the main centre where these were separate services. The Heart Hospital (THH) service was not included in 'catchment' comparisons as this service takes referrals from throughout the UK. The second method calculated service provision in relation to published populations for SHAs and for Wales, Scotland and Northern Ireland (Office for National Statistics 2006). As the population in South East Coast SHA has no specialist service and looks to London for this service, this population was amalgamated with the London population; service information for all the London centres, including the Heart Hospital, was included to calculate rates of provision in relation to combined London and South East Coast SHAs.

5.3 Results

Replies to the initial questionnaire were received from all 24 regional genetics services. The initial questionnaire identified 17 specialist ICC services, 1 service (Edinburgh) that offered a Marfan service that was not within a broader ICC service and 1 Marfan service that was organised so that it spanned two areas – SW Thames and NW Thames.

All 19 specialist ICC/Marfan services completed the more detailed follow up description of their service and all respondents provided detailed responses to our further questions to validate the data. An

additional service which had initially indicated that it did not meet the criteria for inclusion as an ICC service later completed the follow up questionnaire bringing the total number of ICC/Marfan services completing a questionnaire to 20. Five of the 20 services completed a separate questionnaire on their Marfan service – for 3 of the services (West Midlands, Oxford and Scotland Grampian/Aberdeen) this was in addition to the questionnaire on the other ICC services. For the purposes of examining service provision, the Marfan service activity was incorporated into the figures for broader ICC services in the 3 areas that completed 2 questionnaires. For the Marfan service which spanned 2 areas, activity was divided into the activity for each of the areas it served (St George's in SW Thames and Brompton/ Harefields in NW Thames) as this service was able to indicate which parts of its service and activity related to each of the two ICC services. The results of the survey are presented below for 19 services: 18 combined ICC/Marfan services and 1 Marfan only service (Edinburgh).

Four services (Devon and Cornwall, Nottingham, Leicester and Tayside) indicated that they did not have a specialist ICC service – although in two cases (Leicester and Tayside) it was noted that a specialist service was under development. Finally, replies were not received on the follow up questionnaire from 1 of the identified services: the Marfan service in Glasgow (although information was received from the other parts of the ICC service in Glasgow). The findings are detailed in the following sections. For consistency services are displayed in all tables in the standard order of SHA, followed by Wales, Scotland and Northern Ireland.

5.3.1 Services and population served

Table 5.1 provides information on whether specialist services were identified in each Strategic Health Authority.

Table 5.1 Service information

Region (Population)	Service/hospital base	Geographical area served	Catchment population (million)	Specialist service
North East	Northern Genetics Service	Northumberland, Tyne & Wear, County Durham, N. Cumbria, Tees Valley	Just over 3	Yes
North West	Manchester Royal Infirmary	Manchester & NW excluding Merseyside	5.5	Yes
	Liverpool Women's Hospital	Cheshire and Merseyside	Up to 2.9	Yes
Yorkshire	Leeds General Infirmary	Yorkshire & Humber- not Sheffield area	3	Yes
	South Yorkshire Cardiothoracic Centre/ Sheffield Children's Hospital	S Yorks., N Derbys., N Notts and S. Humber	1.8	Yes
East Midlands		Notts, Derbys. Lincs	2.3	No
	Glenfield Hospital (University Hospitals of Leicester)	Leics, Rutland parts of Northants. & Notts. (Wider catchment area for congenital heart disease)	1.5 (4.5 for congenital heart disease)	Under develop ment
West Midlands	Birmingham Women's Hospital	West Midlands	5.3	Yes

East of England	Addenbrooke's and Papworth Hospitals	East Anglia	2.5	Yes
London	Guy's, St Thomas' Hospital, Kings College Hospital and University Hospital Lewisham	SE England (NHS London Lambeth, Lewisham and Southwark) & part of NHS SE Coast (East and West Kent & E Sussex)	4	Yes
	St George's Hospital	SW Thames/National	2.5	Yes
	Kennedy Galton Centre, St Mary's and Brompton Hospitals	London NW Thames, Herts. & Bedfordshire	3.7	Yes
	London Chest and St Bartholomew's Hospitals	NE Thames Region	3-4 million	Yes
	The Heart Hospital (THH)	North Central London and National referral	1.8 (UK wide referrals for inherited conditions)	Yes
South East Coast		Kent, Surrey and Sussex	4.2	No service
South Central	Oxford Radcliffe Hospital	Oxfordshire, Bucks, Wilts, Berks, and Northants.	3.5	Yes
	Southampton			No
South West	Peninsula, Exeter	Devon and Cornwall	1.6	No
	Bristol Congenital Heart Centre	Avon, Somerset, W Wilts and Gloucs.	2.6	Yes
Wales	University Hospital of Wales, Cardiff	Wales	Approx. 3	Yes
Scotland	Western General Hospital, Edinburgh	SE Scotland, Lothian NHS Hospitals Trust	1.2	Yes
	Royal Alexandra Hospital	W Scotland, Greater Glasgow and Clyde	2.5	Yes
	Dundee	Tayside	0.45	No
	NHS Grampian Scotland (North of Scotland Regional Genetics Service, Aberdeen)	Grampian, Highlands, Orkneys, Shetland and W. Isles	0.83	Yes
Northern Ireland	Belfast Health & Social Care Trust (Royal Victoria Hospital)	N Ireland	1.7	Yes

From the above table it can be seen that most regions have a specialist service, with the exception of the East Midlands and the South East Coast. It should be noted that much of the South East Region is served by the London hospitals and that services are being developed in Leicester and Nottingham for the East Midlands. There is no service in Tayside and services in Edinburgh are limited to a Marfan service. In London there are a number of specialist services, a national centre (The Heart Hospital) receives referrals for ICCs from across the UK and in addition, St George's Hospital and Kings College Hospital in London also receive referrals for ICCs from across the UK.

A number of services did not have a specialist ICC service but patients with cardiac conditions were seen in the general genetics service or the general cardiology service (Peninsula, Nottingham and Tayside). Some genetics services had some aspects of their service working jointly with the cardiology services but many of the services operated independently (for example in North West Thames).

Catchment populations for services ranged from less than half a million in Tayside to 5.5 million in the North West and 5.3 million in the West Midlands. Most services served a catchment population of 1–3 million (13 of the 25 services), 8 served a population of 3–5 million and two services each served a very small population (under a million) or a particularly large population – over 5 million. The services that do not have a specialist ICC service tend to serve populations of between 1.5–3 million (with the exception of Tayside which served the smallest population of less that half a million).

Table 5.2 Location and Overview of Service

The following overview of the services available in each part of the UK was provided by the ICC services:

North East (Newcastle)

The Northern Genetics Service (NGS) is commissioned at regional level to provide a range of genetics services to Northumberland, Tyne & Wear, County Durham, Teesside and North Cumbria. The service is based at the International Centre for Life in Newcastle upon Tyne, with a satellite unit at James Cook University Hospital in Middlesbrough. The service includes a mixture of multidisciplinary and parallel cardiac/genetics clinics. Cardiology management issues are devolved to stand alone cardiology clinics. NGS has recently recognised cardiac genetics to be a growth area requiring service development in collaboration with the North of England Cardiovascular Network. The clinical lead for cardiac genetics was appointed in 2003 and has led the change from a single mixed tertiary cardiac genetics clinic to the following, providing a framework of tertiary clinics on almost a weekly basis:

- ***Cardiovascular connective tissue disease clinic***

Site: Freeman Hospital, Newcastle
Frequency: monthly
Type: adult and paediatric Marfan syndrome and related disorders; in parallel with paediatric cardiology and GUCH clinic; also in parallel with cardiology / obstetric clinic.

Access to echo for children is sometimes a problem in Newcastle.

- ***Adult Inherited Heart Disease clinic***

Site: Freeman Hospital, Newcastle
Frequency: monthly
Type: adult cardiomyopathy / arrhythmia / sudden death; run jointly with arrhythmia cardiologists

- ***Inherited Cardiovascular Disease clinic***

Site: James Cook University Hospital, Middlesbrough
Frequency: monthly
Type: mixed adult Marfan syndrome, cardiomyopathy, arrhythmia / sudden death; run jointly with an adult cardiologist with additional input if required

Table 5.2 continued

- ***Paediatric cardiac genetics clinic***

Site: James Cook University Hospital, Middlesbrough
Frequency: quarterly
Type: children's echo clinic (Marfan syndrome and cardiomyopathy); run jointly with a paediatrician with local lead for paediatric cardiology and trained in echocardiography

CARDIGEN network
During 2007, the relationship between cardiac genetics and cardiology across the North of England Cardiovascular Network was strengthened by the creation of a hub and spoke network. The network aims to formalise communication links, optimise patient flow and standardise management. Key features of the network are:

- two hub centres (Newcastle upon Tyne and Middlesbrough), which host tertiary cardiac genetics clinics
- ten district cardiology services (spokes) with local leads for inherited cardiovascular disease
- network-ratified guidelines for referral of patients to tertiary centres
- network-ratified guidelines for management of patients and families – this includes cascade surveillance, which has been devolved to district units.

Northwest (Manchester)

The Manchester service is run as a multidisciplinary service from the Manchester Royal Infirmary. It is aimed at familial sudden cardiac death syndromes (including cardiomyopathy) and concentrates on adults, with links to paediatrics. The model of service in cardiac genetics in Manchester has been developed and strengthened following close liaison between cardiac and genetic services established as a consequence of a successful DH cardiac genetic service development bid in 2005-2007. Ongoing 6 monthly meetings between cardiology and genetics consultants formalise communication links and ensure that the service delivery pattern is equitable and meeting patient needs.

The cardiac genetics service includes:

1. Regular genetics clinics conducted at St Mary's Hospital, Royal Manchester Children's Hospital, Blackpool Victoria Hospital, Burnley General Hospital, Lancaster Royal Infirmary, Macclesfield District General Hospital and Royal Albert Edward Infirmary Wigan. These are undertaken by two consultant clinical geneticists specialising in cardiac genetics and both children and adults patients are seen. This provides for a wide range of cardiac conditions including LQT and other arrhythmias, SCD, cardiomyopathies, Marfan syndrome and familial aneurysm and congenital heart disease with approximately 250-300 patients seen per year.
2. Multidisciplinary familial SCD clinic at Manchester Royal Infirmary run by consultant specialist cardiac electrophysiologist and genetic counsellor with special interest and expertise in inherited cardiac disease and supported by consultant clinical geneticist. There are currently 2 clinics per month with plans to increase this to 3-4 per month. Focus is on adult patients but with close links to paediatric cardiology.
3. Monthly clinic by genetic counsellor with special interest and expertise in inherited cardiac disease

Manchester Royal Infirmary is a designated GUCH centre and there are close links between the GUCH team and clinical genetics. There are monthly GUCH clinics though not currently attended by a geneticist.There are close links to paediatric cardiology at RMCH and ward consultations are provided for neonates with congenital heart disease.

Table 5.2 continued

Manchester Royal Infirmary is a designated GUCH centre and there are close links between the GUCH team and clinical genetics. There are monthly GUCH clinics though not currently attended by a geneticist.

There are close links to paediatric cardiology at RMCH and ward consultations are provided for neonates with congenital heart disease.

The Fetal Management team includes input from a paediatric/fetal cardiologist and clinical geneticist and meets weekly to discuss cases.

Mersey and Cheshire

Inherited Cardiac Conditions (ICCs) are seen in a selection of genetics clinics. Referrals are accepted from a wide range of sources and then seen either in dedicated genetics clinics for congenital heart conditions, Marfan syndrome, connective tissue and vascular disorders or in joint management / discussion clinics with specialist cardiologists (at the Liverpool Heart and Chest Hospital LH&CH) for families with sudden death or suspected inherited arrhythmias and the cardiomyopathies. Congenital heart and paediatric conditions clinics are parallel with paediatric cardiologists while people with Marfan syndrome, connective tissue and vascular disorders are seen in stand alone genetics clinics. Families with sudden death or suspected inherited arrhythmias and the cardiomyopathies are seen in multi-disciplinary clinics with cardiologists at the LH&CH.

Inherited cardiac genetics clinics are held both centrally in Liverpool (Alder Hey Children´s Hospital, Royal Liverpool University Hospital for adults and joint with adult cardiologists at the LH&CH) and through a network of peripheral genetics clinics to see families with ICC conditions in Chester, Warrington, Ormskirk and on the Wirral. The service has dedicated adult and paediatric clinics that will also see their relevant family members.

Yorkshire (Leeds)

The joint Genetics/Cardiology clinic was established in 1995 in response to the growing number of patients referred to both the genetics and paediatric cardiology services. Since then the rise in patient referrals for all ICCs including Marfan and cardiomyopathy has continued. The team expanded with the publication of NSF Chapter 8 when strong links were developed with the West Yorkshire Cardiac network which has adopted a hub and spoke model for adult cardiac services.

The Inherited Cardiac Diseases clinic (ICDC) is held on a weekly basis at Leeds General Infirmary in the cardiac outpatients. The clinic provides a comprehensive service for families with an inherited cardiac disease. There is a clinical meeting prior to the clinic to discuss cases. There is access to ECGs and echocardiography for children and adults on the day. The team consists of cardiology, genetic and counselling personnel and has a wider support network for patients from the specialist congenital cardiac staff which includes a consultant echocardiographer, adult and paediatric liaison nurses and physiotherapist as well as the Arrhythmia and ICD nurse specialists. In view of the rise in the referrals to the clinic a further clinic was established at York District Hospital. It is held on a monthly basis and has access to ECG and echocardiography for adults. The paediatric cardiology and genetics services cover a large area and to improve the service there are plans to establish an ICDC in Hull. The first phase is a paediatric cardiology/genetic clinic based at Hull Royal infirmary with access to ECG and echocardiography services for children. The second phase will be the introduction of an adult ICDC. The clinic has established referral pathways and close links with the coroners and pathologists.

S Yorkshire (Sheffield) *Table 5.2 continued*

The Regional Inherited Heart Disease Service in South Yorkshire is led by the consultant cardiologist. It was set up in 2000 and is now very well established. It was one of the first dedicated services outside of London and sees a wide range of ICCs. It serves South Yorkshire and North Derbyshire, covering the surrounding areas as well as receiving other referrals from outside this region. It provides for a large range of inherited cardiac conditions including the various cardiomyopathies (hypertrophic, dilated, restrictive, ARVC and other rarer cardiomyopathies such as Fabry disease, amyloidosis etc), ion channel disorders such as LQT, Brugada, CPVT and also Marfan and Ehlers Danlos syndrome, familial aortic aneurysm and aortic dissection, cardiac disorders related to muscular dystrophies and families affected by sudden arrhythmic death syndrome. The service works in a multidisciplinary fashion. Currently 4 inherited heart disease clinics are held per week at South Yorkshire Cardiac Centre, with additional sessions being held at the associated North Trent Clinical Genetics Service. A large number of referrals are received from general practice, other physicians and cardiologists as well as from the coronial service in cases of sudden death evaluation. The specialist inherited heart disease service includes a dedicated cardiologist, specialist nurses, regular MDT meetings with clinical geneticists and genetic counsellors. There is specialist aortic surgery, electrophysiology, echocardiography and cardiac MRI on site as part of the service.

There are clinics at the South Yorkshire Cardiothoracic Centre and Sheffield Children's hospital. Patients aged 13 upwards are seen at the Cardiac Centre and patients of all ages are seen at the Sheffield Children's Hospital Genetics service. There is paediatric cardiology input.

E Midlands

Integrated cardiac genetics service (Glenfield Hospital, Leicester) was developed in 2007-8 both to formalise existing services within genetics and cardiology and to optimise referral, investigation and management pathways for patients / families affected by cardiomyopathies, sudden cardiac death/ channelopathies and Marfan syndrome. Monthly MDT 'clinics' set up with consultant geneticists, paediatric and adult cardiologists and electrophysiologists as well as a nurse counsellor. Cardiac investigations and reviews performed at Glenfield Hospital, genetics clinics at Leicester Royal Infirmary / home visits. Further service development / investment ongoing. Major established BHF funded research programmes for genetic basis of common cardiac conditions and of congenital heart disease. A service is also currently being set up at Nottingham City Hospital.

W Midlands (Birmingham)

The service includes a LQT clinic (including provision for SADS referrals), cardiomyopathy clinic, GUCH disease clinic, paediatric cardiac clinic and multi-condition cardiac clinic. LQT, cardiomyopathy and GUCH clinics are all multidisciplinary. The paediatric cardiac clinic is currently stand-alone but development plans include a joint paediatric arrhythmia clinic. The multi-condition clinic runs on a stand alone basis for patients not in any of the other clinics above. All clinics are held centrally and both adults and children are seen. There is a monthly genetics Marfan clinic, of which at least 4 a year are joint cardiogenetic multi-disciplinary clinics where both adults and children are seen. The clinics are held centrally but Marfan patients are also seen in peripheral settings.

East of England (Cambridge) *Table 5.2 continued*

The Eastern Region Genetics service is commissioned to provide genetics services to a core population of over 2.5 million in East Anglia, but in addition genetic services are provided to some patients from Herts., Beds., Essex and Lincs., bringing the potential catchment population for the Cardiac Genetics service to nearly 5 million. The cardiac genetics service was established in 1999.

- **cardiac genetics clinic** – site: Addenbrooke's Hospital, frequency: monthly. This is a clinic for inherited cardiac disorders and comprises a consultant cardiologist, a consultant clinical geneticist, a specialist trainee in genetics, a genetic counsellor, a genetics nurse and from Dec '08 a BHF cardiac genetics nurse. There is a monthly cardiac genetics team meeting.
- **cardiac genetics EP clinic** – site: Addenbrooke's Hospital, frequency: quarterly (planned increase to monthly from April '09). A consultant electrophysiologist joins the multidisciplinary team listed above to see patients with a family history of SCD, arrhythmia or cardiomyopathy.
- **GUCH and inherited cardiac disorders clinic** – site: Papworth frequency: monthly. This clinic is staffed by two consultant cardiologists.
- **Paediatric cardiac genetics service** – site: Addenbrooke's, frequency: as needed. A named paediatric cardiologist and named cardiac geneticist provide paediatric cardiac genetics service on an 'ad hoc' basis and are embedded within the team providing the monthly cardiac genetics service.

East Anglia cardiac genetics steering group – This is a group of specialists from around the region comprising cardiologists, electrophysiologists, clinical geneticists, paediatric cardiologist, genetic counsellor, public health genetics, specialist cardiac pathology, cardiac network representative which meets several times a year to develop the regional cardiac genetics service.

London NE

This is a new and developing service which has grown by 200% in the last year. This has required a restructuring of services. Formal clinical pathways are in development, as are provisions for greater involvement of specialist nurses and electrophysiologists. The focus is on cardiomyopathy principally HCM. Out of 8 clinics per month, one is multidisciplinary at present. The service is centrally located and aimed at adults.

London NW

There are joint genetic cardiac centrally located clinics for arrhythmia and cardiomyopathy at St Mary's hospital and The Brompton hospital cardiology units, with on site investigations, such as cardiac echocardiography. There is a general genetic service for Marfan syndrome (see also London SW), inherited congenital heart diseases, connective tissue and vascular syndromes in children and adults. Other conditions and syndromes are seen in central and satellite general genetic clinics. The clinics are for adults, children and families.

London SE

Table 5.2 continued

Guy's and St Thomas' Hospital

General Cardiac Genetics Clinic (GCC) is aimed at all family members and the Inherited Cardiomyopathy Clinic (ICMC) is aimed at adults. Each clinic is held monthly. The GCC clinic was started to provide follow-up for mostly Marfan syndrome patients and families but more recently has been redeveloped for more complex inherited cardiac conditions requiring multidisciplinary care and discussion.The GCC is attended by a genetic counsellor, consultant geneticist(s), SpR, consultant paediatric cardiologist, consultant adult cardiologist. The ICMC is attended by consultant cardiologist, genetic counsellor, specialist cardiac nurse, Echo and ECG technicians. The GCC is held in Clinical Genetics Dept Guy's hospital. The ICMC is held in Cardiac Outpatients Clinic at St Thomas'.

King's College Hospital and University Hospital Lewisham

There are 2 inherited cardiac diseases clinics per week dedicated to the management of inherited cardiomyopathies and ion channel disorders. The clinics take place at King's College Hospital and University Hospital Lewisham) averaging 22-24 patients between them including 1 sudden adult death victim family. In addition there is a monthly, inherited heart muscle disease clinic (average 14 patients) operating at St Thomas' hospital (mentioned above) and plans are currently in progress to expand the clinic to a once weekly basis. All 3 clinics are multi-disciplinary and receive input from 3 cardiology research fellows in cardiomyopathy or ion channel disorders, 1 cardiology specialist registrar, 2 consultant electrophysiologists, 1 professor in cardiac MRI, 2 BHF arrhythmia nurses, 1 heart failure nurse, 5 dedicated cardiac physiologists, 1 geneticist, 2 cardiac paediatricians, 1 cardiac pathologist and 2 geneticists. The clinics are consultant led and receive referrals from all over the UK. The clinics are run on a one-stop-shop model and all non-invasive investigations and ajmaline provocation tests are performed on the same day at all 3 hospitals with the exception of cardiac MRI, which takes place at St Thomas' hospital. All patients are assessed by an expert consultant cardiologist, trained in the diagnosis, risk stratification and management of complex cardiomyopathy and ion channel disorders. The clinics are heavily supported by cardiology research fellows, specialist nurses and cardiac physiologists. Both King's and St Thomas' have supporting electrophysiologists for ICD implantation. Families with young children are preferentially directed to St Thomas' due to the excellent paediatric cardiology support. Genetic counselling and venesection for future genetic analysis is performed at all 3 sites by geneticists from St Thomas' hospital and St George's hospital. The 3 separate clinics held at King's, University Hospital Lewisham and St Thomas' share the same database, CMR facilities, paediatric cardiologists and geneticists (all provided by St Thomas's hospital).

The clinics are aimed at all individuals who may have an inherited cardiomyopathy or ion channel disorders but also evaluate individuals with hereditary neuro-cardiac syndromes, coronary anomalies and Marfan syndrome. Given their expertise and links with the Olympic medical institute, the clinics at King's and UHL are asked to evaluate highly trained athletes with suspected cardiac disorders.

London SW *Table 5.2 continued*

There is a weekly multi-disciplinary clinic staffed by a consultant, SpR, arrhythmia nurse and genetic counsellor. There are monthly additional parallel clinics with a paediatric cardiologist and clinical geneticist. The clinics are held centrally at St George's and aimed at adults and children. Marfan and overlapping conditions, for example any aortic aneurysms, are seen in Marfan clinics held at St George's which run simultaneously and in parallel with the cardiac out patients clinic. Clinics are also run at the Brompton and Harefields Hospitals in conjunction with London NW. Both adults and children are seen.

London, The Heart Hospital (THH)

The service consists of a number of specialist condition clinics including cardiomyopathy, inherited arrhythmia and Marfan syndrome clinics. The majority of the group's outpatient activity focuses on the evaluation and counselling of patients and families in disease specific clinics at THH and Great Ormond Street Hospital (GOSH). All clinics use a common template modified for specific conditions: pre-screen pedigree analysis→ ECG/Echo/CPEX/SAECG → Nurse specialist → Consultant → DNA blood test/family screening/ICD counselling/surgery. In families affected by SCD, death certificates, post mortem reports and where possible stored tissue and DNA are collected for histological review and genetic analysis. All new patients undergo electrocardiography, echocardiography and exercise testing on the day of their clinic visit. After the investigations, patients are seen by a nurse specialist or genetic counsellor who provides information on their condition and obtains consent for genetic testing. Patients are then assessed by a consultant cardiologist and a management plan is drawn up. Genetic testing is performed either at the Institute of Child Health (GOSH), John Radcliffe Hospital or AMC medical centre in Amsterdam. The service receives referrals from all over UK with over 1,000 new patients per year and 3,000 follow up attendances. Pedigrees are stored on a Cyrillic database.The service is centrally located at THH and GOSH with telemedicine links to Glasgow and Belfast. Consultant support is provided for a monthly ICC clinic at St. Thomas's Hospital in London and is aimed at children and adults.

South Central (Oxford) *Table 5.2 continued*

The Oxford regional genetics service is specially commissioned to provide a range of genetic services to a population of over 3 million, centred on the Thames Valley and surrounding areas including Buckinghamshire, Northamptonshire, Berkshire and Wiltshire. The service is based at the Churchill hospital in Oxford. A tertiary level cardiac service is based at the John Radcliffe Hospital in Oxford, as is the University Department of Cardiovascular Medicine.

The cardiovascular genetics service has developed two complementary arms: the Marfan syndrome and Inherited Cardiac Disease clinics. Both clinical services are backed by laboratory genetic services, with the Oxford regional genetic laboratory being a major provider of cardiovascular genetic services to other UK centres.

The Inherited Cardiac Disease Service

The Department of Cardiovascular Medicine has an international reputation for basic and clinical research in the field of inherited cardiovascular disease. Close links between the Department of Cardiovascular Medicine and the NHS Clinical Genetics department have led to the development of a fully funded clinical service for patients with inherited cardiomyopathies and arrhythmogenic syndromes. The clinical service has been recognised locally and nationally as a flagship for cardiovascular genetics and as such has benefited from funding from the Oxford Genetics Knowledge Park and Biomedical Research Centre and has contributed to the development of national guidelines for the management of patients with inherited cardiovascular disease.

The cardiac genetics clinics take place on a weekly basis. Each clinic is served by a specialist cardiologist, two registrars/lecturers, and a dedicated full time genetic counsellor. A consultant clinical geneticist attends one clinic per month. A paediatric cardiologist with a specialist interest in inherited cardiomyopathy attends one clinic per month. An additional full time genetics counsellor is funded to provide dedicated research support and a BHF Genetics Nurse joined the service in late 2008. Monthly MDT meetings are attended by clinical cardiologists and electrophysiologists, a consultant clinical geneticist and a specialist genetic counsellor. Weekly service laboratory liaison meetings are held between the cardiovascular genetic clinical team and the laboratory staff. Weekly research seminars are held to discuss new findings and ideas. The clinical team meets and works with the local specialist commissioning team to further develop services.

Marfan syndrome service

The Marfan syndrome service is well established in Oxford, having been run as an MDT clinic for almost 15 years. The Marfan syndrome clinic is provided on a monthly basis at present (the service will be applying to the specialist commissioners to increase service provision). Each clinic is served by a consultant clinical geneticist, a genetic counsellor, a consultant cardiologist with a special interest in Marfan syndrome, a consultant medical ophthalmologist and a consultant rheumatologist who has an active research program in inherited rheumatologic disease. As well as providing a clinical service to patients with Marfan syndrome and assessment of patients thought to be at risk, there is an active research interest in cardiovascular MRI imaging and vascular physiological assessment in the cohort of patients with confirmed Marfan syndrome. The service has an expressed interest in participating in multi-centre trials of new pharmacological treatments in Marfan syndrome patients.

South West *Table 5.2 continued*

There is a paediatric Marfan clinic run in the cardiology unit with input from a consultant cardiologist and consultant clinical geneticist. Support is given from the clinical genetics service and paediatric cardiology clinical nurse specialists. In addition there is a full diagnostic and interventional paediatric arrhythmia service with input from 2 consultant cardiologists. There are additional clinics for Barth Syndrome run jointly by a cardiologist and paediatrician.

A cardiac genetics clinic for adults is in operation. This is primarily for patients with Marfan syndrome but also includes patients with inherited cardiomyopathy, cardiac channelopathy and inherited arrhythmia disorders. This is run in conjunction with the clinical genetics service.

There are specialist clinics for both children and adults with pulmonary hypertension. This service is held in conjunction with Great Ormond Street pulmonary hypertension service (children) and The Hammersmith Hospital, London.

Services are multidisciplinary with a multi-disciplinary paediatric Marfan syndrome clinic, Barth syndrome clinic and pulmonary hypertension clinic where patients are seen by cardiologist and clinical geneticist (Marfan), paediatric metabolic physician (Barth) and cardiologist from the national Paediatric Pulmonary Hypertension service (PHT). In the adult cardiac genetics service and paediatric arrhythmia services, the clinical genetics and cardiology clinics are closely linked but not on a single site or contemporaneous. The adult services are supported by 2 recently appointed arrhythmia care coordinators (BHF funded). The paediatric clinics are held in Bristol Royal Hospital for Children. Adult clinics are held in Bristol Royal Infirmary and there are separate (but linked) services for children and adults. The new Bristol Heart Institute is due to open in August 2009. It is hoped that the increased flexibility of outpatient facilities will enable a single stop cardiac genetics clinic to be developed.

Wales (Cardiff)

The service is multi-disciplinary. However, currently cardiac genetic clinics run parallel to general genetics and cardiology clinics with special interest in cardiomyopathy and arrhythmias. There is a separate specialist multi-disciplinary lipid service which forms part of the broader cardiovascular genetics service. The cardiac clinic is held twice monthly at the Institute of Medical Genetics of the University Hospital of Wales. This clinic covers South Wales and the Gwent region of Wales. It is envisaged to have satellite clinics in future to cover other parts of Wales. The clinic is aimed at both adults and children. There is a separate Paediatric Marfan clinic held in Cardiff. At present the Cardiff-based cardiovascular genetics service can only offer a basic core cardiac genetic service. The service lacks funding for expansion and development.

N Scotland (Aberdeen)

The service focuses on Marfan syndrome, arrhythmia, and cardiac genetics. It is multidisciplinary for children with Marfan syndrome and all patients with arrhythmia. It is stand-alone for other patients. The clinics are networked and cater for both adults and children.

W Scotland (Glasgow) *Table 5.2 continued*

The service focuses on cardiomyopathy (including neuromuscular conditions that affect the heart) and arrhythmia and will see rarer genetic referrals if the heart may be affected. The current service is provided on 2 sites and takes referrals from health boards within the West of Scotland (population of 3 million). A weekly clinic is held at the Western Infirmary Glasgow. It deals mainly with patients or their relatives referred from the National Heart Failure Service in the Royal Infirmary Glasgow. It is attended by a cardiologist, a SpR clinical geneticist and a heart failure nurse who has developed a special interest in this area. Thus the focus in this clinic is the cardiomyopathies that lead to heart failure.

A second clinic is held every third week at the Royal Alexandra Hospital in Paisley. This is attended by the same cardiologist, along with a consultant geneticist, a genetic associate specialist with an interest in myotonic dystrophy and 2 nurse specialists, one with an interest in neuromuscular disorders. The focus at this clinic is therefore neuromuscular disorders which frequently affect the heart as well as skeletal muscles.

These clinics are supported by a grant from the Cardiomyopathy Association to employ a nurse specialist and an administrator support officer. Both clinics are supported by a clinic co-ordinator. The existing activity will be rationalised and provided at the new regional cardiac centre – the Golden Jubilee National Hospital. The service started on the 1st of May 2008. There will be 2 clinics per week to provide a service for patients with Inherited Cardiac Conditions. The following is a synopsis of the referral criteria to the proposed service.

- adult patients only (>16 years)
- patients from the West of Scotland with neuromuscular diseases which also affect the heart (mainly muscular dystrophies).
- Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM) and other possible genetic causes of heart failure.

The National Services for Scotland has funded a national network for familial arrhythmias which will include the appointment of genetic nurse specialists. Details still to be published but this will fill a major gap in service.

E Scotland (Edinburgh)

A multidisciplinary Marfan service is in operation for both adults and children at the Western & Royal Hospital for Sick Children.

N Ireland

The genetics service is currently a stand alone service although proposals for a combined cardiac genetics service have been submitted. The service is focused on cardiomyopathy – HCM, DCM, ARVC and Fabry; channelopathies – LQT, Brugada, CPVT; Turner syndrome; Marfan syndrome and family screening where there has been a sudden death. Currently most patients with genetic diseases limited to the heart are seen at cardiology clinics only. Those with multi-system involvement are managed by the genetic service. The Inherited Cardiac Diseases clinics are held in the Royal Victoria Hospital (RVH). Some younger patients are seen at the Royal Belfast Hospital for Sick Children. The genetics service is run from Belfast City Hospital with outreach clinics in the 4 health boards. All these hospitals are now part of a single large Trust (Belfast Health and Social Care Trust). Mainly adults are seen but children are seen in conjunction with consultant paediatric cardiologists.

5.4 Comparative information on service provision

The following sections provide comparative details of those services that have a specialist inherited cardiac conditions service.

5.4.1 The Heart Hospital (THH)

Originally the National Heart Hospital, THH, which is part of University College London Hospitals Trust, provides a specialist service that receives referrals from across the UK. Its analyses of referral information for 2007/8 show that less than half of the patients seen (39%) came from 31 PCTs within the London SHA. The majority of the patients referred to THH came from outside London, from across the UK. As a result, providing information on THH's services by per million catchment population is of limited value as it serves a population well beyond its North Central London catchment population. Information on the levels of services provided by THH is described in the different sections of the text.

5.4.2 Provision of outpatient sessions

Services were asked how many outpatient sessions, counted in half days, were held per month. The responses indicated a wide variation in provision, from 1 to 44 per month. The service providing 44 sessions was The Heart Hospital (THH); as this is a specialist heart hospital providing a national service, it cannot be directly compared with other services. If this service was excluded, the range was from 1 to 15.5, with an average of 7 clinics per month and a median of 5. One service (Northern Ireland) also noted that, although 8 sessions are provided, only 4 are explicitly funded as ICC clinics and the other 4 are cardiology clinics in which a high proportion of patients (75%) have ICCs. The total number of sessions provided per month across the whole of the UK is 167, of which 59% are provided in London.

Variation in provision persists when this is related to catchment population and to SHA/regional population. Excluding the sessions provided by THH, the number of outpatient sessions provided per month per million catchment population ranges from 0.55 to 7.78 with a median of 1.43. This equates to a 14 fold variation in service provision. When the numbers of sessions are related to SHA/regional population, outside London and the South East Coast there is a 11 fold variation from the regions with the lowest (0.4 per million) to the highest (4.6 per million) provision. If London and the South East Coast is included (8.5 per million) the variation is 21 fold.

It should be noted that it is difficult to compare service provision directly and that not all outpatient sessions are providing services exclusively to patients with ICCs. To provide an indication of the degree of variation in the type of services being surveyed, each service was asked to indicate whether all patients seen in the clinics were being seen for genetic conditions. A third of services noted that a proportion of the patients attending the clinics were attending for non-genetic conditions. This proportion was small, estimated as no more that 15% of patients by all of these services except for that in Northern Ireland, which estimated that a quarter of patients are attending for non-genetic causes as noted above. This service's clinics were not designated as ICC services but, due to the demand for these services, three quarters of patients were attending these clinics as a result of inherited conditions.

5.4.3 Provision of specialist staff for the ICC service

Services were asked to give details of the average genetic and cardiology sessional input per month by key members of staff including medical consultants, genetic counsellors, specialist nurses, research, or other clinical or non-clinical staff. Results are shown in table 5.3.

Table 5.3 Specialist medical, genetic counsellor and nursing staff supporting clinics - number of half day sessions/month

Location	Consultants	Genetic Counsellors	Specialist nurses	Research Posts	Other clinician	Others
NE Newcastle	17.3	12.5	0	0	0	2
NW Manchester	8	4	4	0	0	2
Cheshire and Mersey	6	12				
Y & H Leeds	8	40*	0	0		40*
Y & H Sheffield	19	8	40***	0	8	8
WM Birmingham	9	0	28	0	0	0
EE Cambridge	15	4	16*	0	4	1
London LCH	14	1	5	0	15	0
London Northwick Pk	19.5	0	4	0	0	0
London Guys, Kings and Lewisham	20	11	10	12	0	22**
London St Georges	24	8	16	0	8	0
London THH	135	56	144****	40		40
SC Oxford	10	40	0	44	0	5
South West	2.33	0	0	0	0	0
Wales Cardiff	10	20	0	0	0	0
Scotland Aberdeen	6	16	0	0	0	0
Scotland Glasgow	12	4	28***	0	4	0
Scotland Edinburgh	1.2	0	0	0	1.3	1.3
N Ireland	16	0	60***	0	0	0

*BHF funded for 3 years
** The nurse posts are not currently funded by the NHS
*** Posts funded by the Cardiomyopathy Association for two years
**** Ongoing Cardiomyopathy Association funding for posts

Chapter 6 provides a description of the range of other clinical and non-clinical staff.

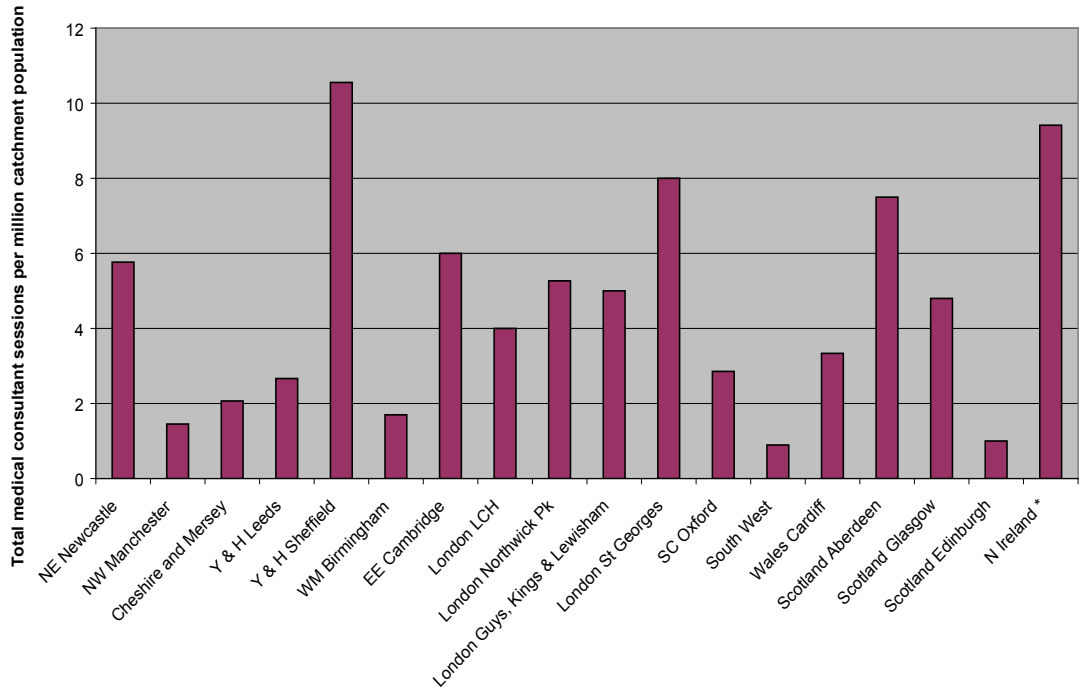
Over the whole of the UK a total of 352 sessions were provided by medical consultants in clinical genetics or cardiology, representing 8.7 whole time equivalents. Of these 60% were in London. For genetic counsellors, the equivalent total numbers were 5.9 whole time equivalents (33% in London), and for specialist nurses 8.9 whole time equivalents (50% in London).

In relation to catchment population (excluding THH) the number of sessions per million provided by medical consultants ranges from 0.9 (South West) to 10.6 (Sheffield) with a median of 4 sessions per million (see Figure 5.1).

There were 37.3 sessions provided by clinicians (other than consultants, genetic counsellors and specialist nurses) of which 62% were in London. The range was between 0 session and 15 sessions. Other non clinical staff provided 121.3 sessions, half of which were in London, and the range for

individual services was between 0 and 40 sessions.

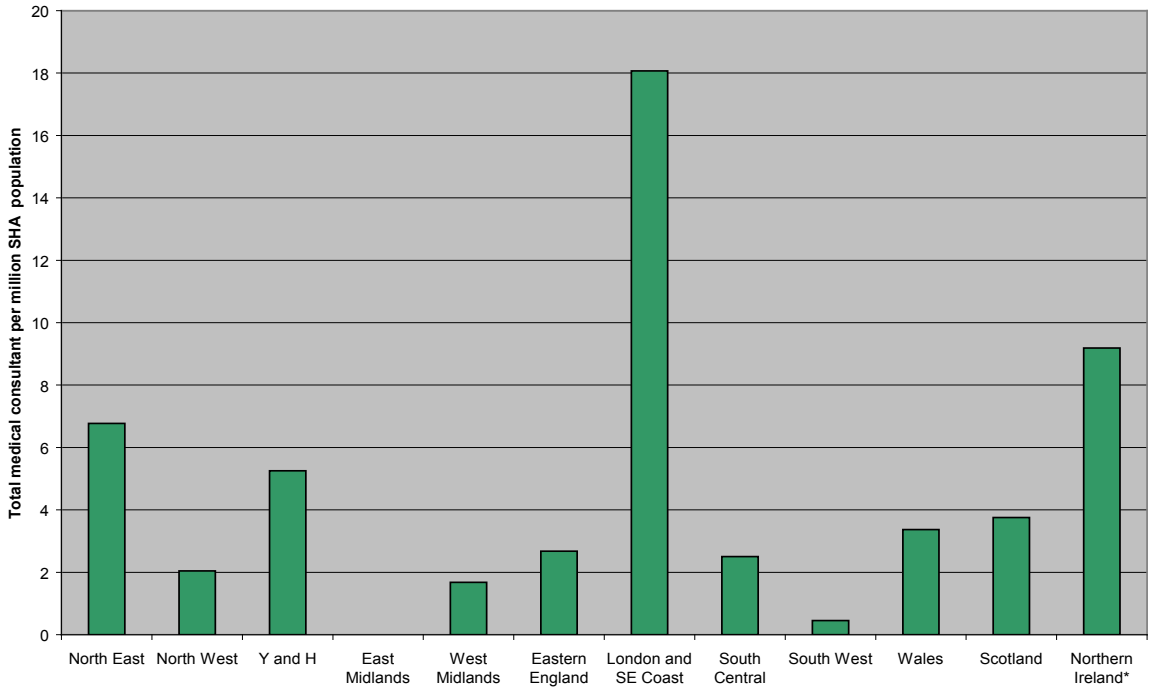
Figure 5.1 Total number of sessions for medical consultants per million catchment population



* Not all sessions in Northern Ireland are designated and funded as ICC services
Sessions from THH have not be included due to the national nature of this service - see paragraph 5.4.1 on The Heart Hospital

In relation to SHA/regional population, the number of sessions provided by medical consultants ranged widely from 0.5 sessions per million population in the South West to 18.1 sessions per million population for London and South East Coast representing a 36 fold variation in consultant sessions (see figure 5.2). Provision for London and SE Coast SHAs was amalgamated as patients in SE coast are referred to London services. Excluding the London and South East Coast figures, there was still an 18 fold variation between the region with the lowest number of sessions per million population (the South West) and the region with the highest number (Northern Ireland). (It should be noted that not all the sessions in Northern Ireland are in the job plan and so there are still resourcing issues of demand not matching the funding in this part of the UK).

Figure 5.2 Total medical consultant sessions per million SHA/regional population



*Not all sessions in Northern Ireland are designated and funded as ICC sessions

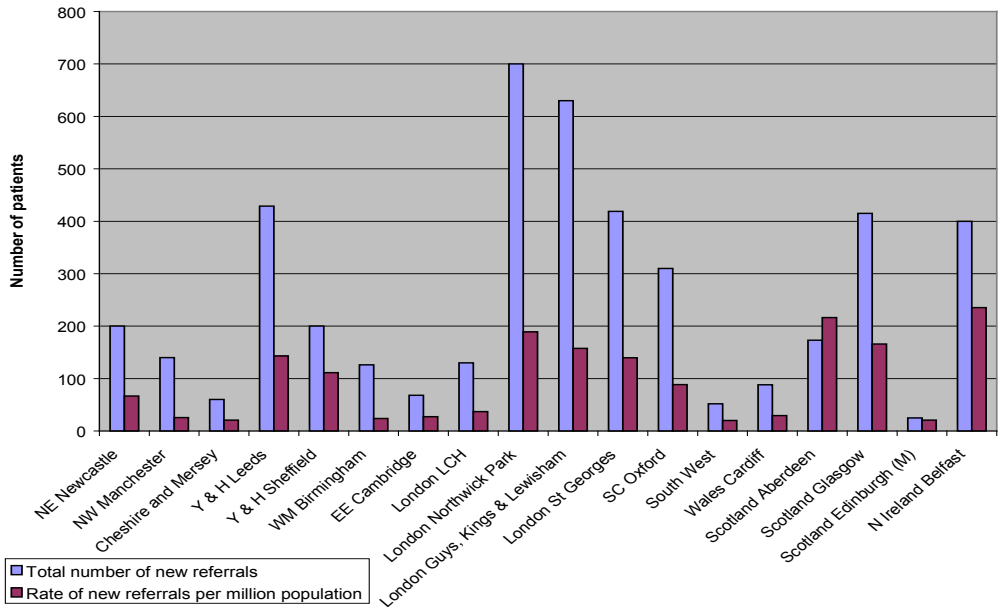
5.4.4 Service activity

Services were asked about the numbers of new referrals, the total number of patients seen and the numbers of families seen during the year 2007–8. Some services found it difficult to provide this information and in particular to estimate numbers of families seen, so data on families have not been used for quantitative comparisons. All data quoted here have been verified by the services concerned.

The Heart Hospital in London, which provides a highly specialist service for the UK, saw by far the greatest number of patients, with a total of 5,628, of whom 1,209 were new patients. Overall, the total number of patients seen in the UK was 14,283, of which 5,774 were new patients. Activity is highly centralised in London, with 64% of total patients and 54% of new patients being seen in the capital.

Figure 5.3 shows the numbers of new patients seen in ICC services and the rate per million of the centre's self-reported catchment population. For services providing services for the full range of ICC conditions (ie not the Marfan only services) the lowest number of new patients seen per year was 52 and the highest outside London was 429. In relation to their catchment population new referral rates vary more than ten-fold from 20 per million in the southwest to 235 in Northern Ireland (see figure 5.3).

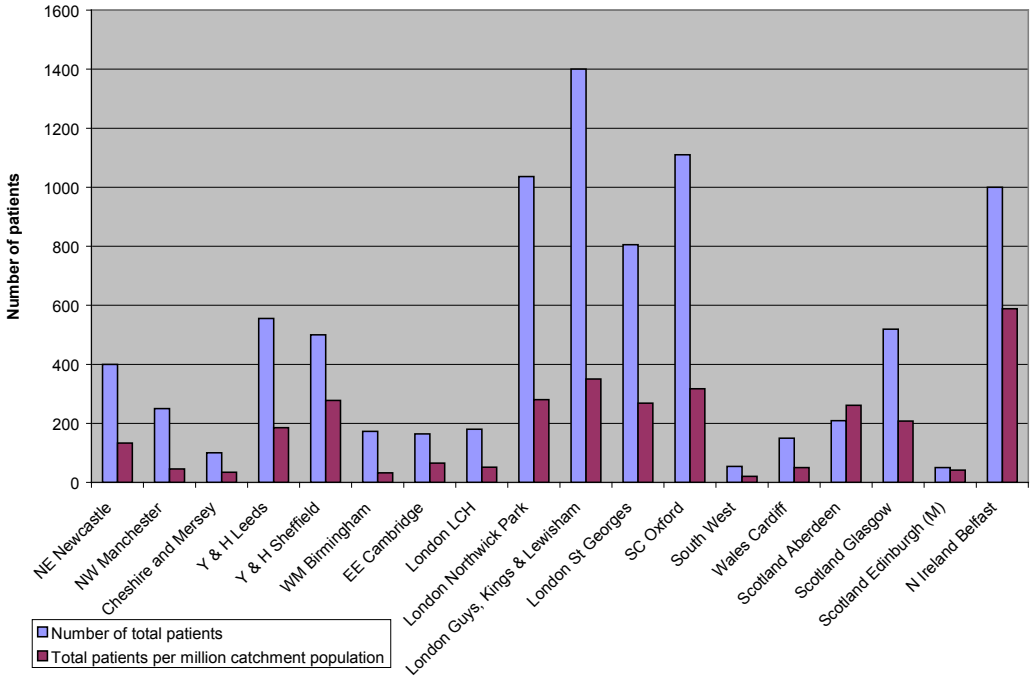
Figure 5.3 Annual estimated number of new referrals and rate per million catchment population



The numbers from THH have not be included due to the national nature of this service - see paragraph 5.4.1 on The Heart Hospital

Similarly, Figure 5.4 shows that the total number of patients seen by services outside London varies almost 30-fold from 21 per million catchment population in the Southwest to 588 in Northern Ireland.

Figure 5.4 Annual estimated number of total patients and rate per million catchment population

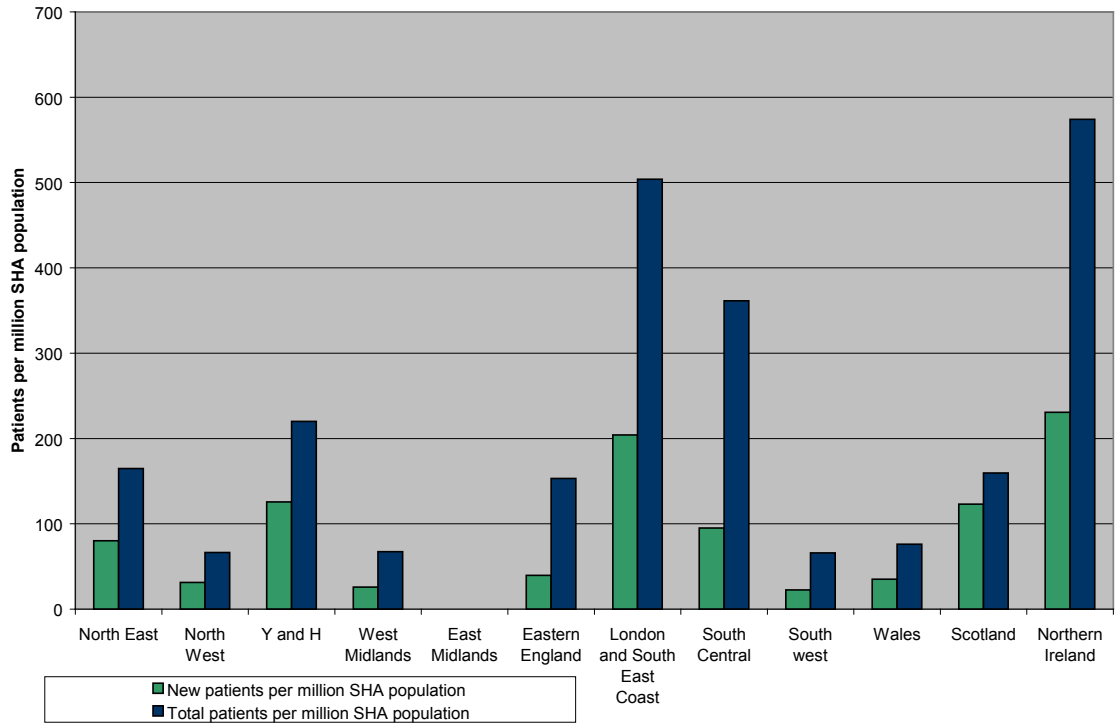


The numbers from THH have not be included due to the national nature of this service - see paragraph 5.4.1 on The Heart Hospital

Comparative rates for services provided to new patients and total patients within a given region were calculated in relation to SHA populations and populations for Wales, Scotland and Northern Ireland. In this calculation, the figures for The Heart Hospital were allocated to the region from which patients were referred and only included in the London and SE Coast SHA where patients were referred from London or SE Coast SHAs. This gives a more accurate picture of the levels of service provision received both by patients living in regions outside of London and also in London compared to other parts of the UK, as in certain SHAs historical referral patterns have resulted in many patients living outside London being seen in London hospitals. The numbers of patients seen are much greater at THH compared to other London centres (the total number of patients seen is 5,628 at THH compared to 3,421 for all the other London services combined). Ideally, the data would also be corrected for other centres in London as a number of these centres also receive referrals from across the UK and so inflate the level of service provision received for patients from London and the SE Coast compared to other parts of the UK. However, these data were not available.

Again Figure 5.5 shows that there is great disparity in provision between geographical areas. The figures show a 10 fold variation in provision from the worst to the best provided region for new patients per million and a 9 fold variation for total patients per million.

Figure 5.5 New patients per million and total patients per million by SHA/regional population



5.5 Estimates of shortfall in service provision

As part of this Review we aimed to provide an assessment of whether services are meeting expected requirements and to estimate the size of any shortfall in service provision. This question can be addressed by:

1. An epidemiological approach, in which current service activity is compared with epidemiological data on the incidence or prevalence of the conditions, or

2. A more empirical approach, based on observed current service provision. Here, the total shortfall in activity is estimated by comparing actual activity with the total activity that would be expected if all services were seeing as many patients per million population as the most active services (which are assumed to be operating optimally).

Both of these approaches have serious limitations, which we discuss below. Nevertheless, we considered it important at least to attempt to estimate the volume of activity that might be expected if all individuals requiring services for ICCs were to receive them.

5.5.1 Epidemiological approach

In theory, any shortfall in service provision could be calculated by comparing the total annual incidence of the conditions with the total number of new patients seen by services each year. In practice, this is not possible because we have no way of estimating incidence for the conditions. The different conditions vary considerably in their penetrance and natural history, with some patients diagnosed early in life and others not until old age, if at all. The nature of the cascade approach also makes the definition of 'incidence' problematic, as some 'patients' who require evaluation will turn out not to have inherited the condition, and many others may lack overt symptoms.

Alternatively, prevalence figures can be used: the total population prevalence of the conditions is compared with the total number of living patients currently known to services. This method is more feasible but also presents problems. Prevalence estimates for the conditions are highly uncertain because the epidemiological data are limited, particularly for the rarer conditions. Here, too, there are problems of definition because it is not always easy to say when an individual 'has' a particular condition, and because the cascade approach mandates investigation of many individuals who turn out not to be at risk (in other words, the total number of individuals who need to be investigated is substantially higher than the total prevalence of the conditions). There are also practical problems in estimating total numbers of patients currently known to services, as only those who were seen by the specialist service within the last year are included in our data.

Nevertheless, a very rough comparison of current service activity with estimates of prevalence suggests a large shortfall in provision. The total (all-age) prevalence of ICCs calculated in Table 2.1 is 220,000 excluding FH. The total number of patients seen annually across the country is about 14,000, suggesting (but with all the caveats discussed above) that there could be at least a 10-fold shortfall in total provision of care for ICCs. The implementation of cascade testing is likely to result in a significant proportion of these people presenting to services within the next 5 years.

5.5.2 Empirical approach based on current service use

Two sets of 'best provided' services were used to calculate the total number of new patients expected nationally per year if all services were working at this level of activity:

1. London services. These services showed the highest activity. However, it is not clear exactly how many of these patients come from the London and South East region, and how many are national referrals from other regions. (THH's activity data only include patients living in London and the SE Coast SHAs but this adjustment has not been made for the other London services as we do not have this data for these services). Total activity for London services: 204.23 patients per million of population

2. Well established regional services outside London. The three English SHAs that provided a service on a formal regional basis were used: Northeast SHA (Northeast service); Yorkshire and Humber SHA

(Leeds and Sheffield services); South Central SHA excluding Southampton, Portsmouth and the Isle of Wight (Oxford service). Total activity for 'best provided' regional services: 110 patients per million of population.

These levels of activity were used to estimate the total number of new patients per year expected across the whole country, or in the regions excluding London and the SE (Table 5.4; see Appendix 3 for details of these calculations). These numbers were then compared with the actual number of new patients seen nationally (5774) or in the regions excluding London (3078), and the estimated shortfalls calculated.

Table 5.4 Estimates of shortfall in service provision

	Whole of UK[1]			Regions (excluding London)[2]		
	New patients expected per year	Actual new patients per year	Estimated current shortfall	New patients expected per year	Actual new patients per year	Estimated current shortfall
Calculated from London 'best rates'	12,376	5,774	6,602	9,967	3,078	6,889
Calculated from regional 'best rates'	6,666	5,774	892	5,368	3,078	2,290

1 Population 60.6 million
2 Population 48.8 million

The shortfall in activity calculated by this method varies widely, from just under 900 to almost 7,000 patients per year. The lower figures are those calculated using the rates from the 'best' regional providers. These figures suggest that, although there is some shortfall in regional services, nationally there is little unmet need, with London services effectively compensating for any deficiencies in the regions. We think this conclusion is unlikely to be justified, however, as all regional services report lack of capacity and resources, and a rapid increase in referrals as they become more established, indicating that they have not yet reached a steady state.

We suggest that the figure of 7,000 patients per year is likely to be a better indication of the true shortfall in current provision. Essentially, this is the increase in activity that would be needed to bring the rest of the country up to the level of provision in London, with its longer established and well resourced services. Reported activity levels in London are inflated by patients referred from elsewhere in the country, thus increasing the apparent shortfall in the regions. However, this would only lead to a serious over-estimate of the national shortfall if London services were meeting all local need as well as some regional need; in view of the very large total shortfall suggested by the epidemiological data, we think this is unlikely.

Thus, our best estimate of the shortfall in service provision for new patients in the UK is approximately 7,000 new referrals per year, representing a required increase of 3-4 fold in regional provision. As these new patients are seen by services there will also be an increased need for services for their review as many patients will need ongoing monitoring. In addition, it could be assumed that each index patient might result, by cascade testing, in a number of family members being identified. Consequently, as

more sophisticated and systematic methods for cascade testing are implemented the numbers of new patients will rise dramatically.

Currently, we have no ready way of estimating how many of these patients will require ongoing specialist care and how many could be managed at primary or secondary care level. As services develop, ongoing monitoring and audit will be important.

5.6 Genetic tests

The genetic tests for cardiac conditions listed by the UKGTN are shown in Table 5.5 with further details of these tests in appendix 4. (The UK GTN provides a Genetic Testing Directory that lists diseases and genes for which UKGTN approved testing is available from UKGTN member laboratories. All the tests listed have been evaluated for clinical validity and utility. The UKGTN and the Genetics Commissioning Advisory Group (GenCAG) recommend, to all UK commissioners and provider organisations, that testing listed in the Directory should be available to their local populations).

Table 5.5 Genetic tests provided and listed by UKGTN laboratories

Disease (OMIM)
Barth Syndrome; BTHS (302060)
Brugada Syndrome (601144)
Cardiomyopathy Dilated, 1A; CMD1A (115200)
Cardiomyopathy Familial Hypertrophic, 2; CMH2(115195)
Cardiomyopathy Familial Hypertrophic, 4; CMH4(115197)
Cardiomyopathy Familial Hypertrophic; CMH(192600)
CPVT (604772)
Ehlers Danlos syndrome Type IV(130050)
Hypercholesterolemia, Autosomal Dominant (143890)
Hypercholesterolemia, Autosomal Dominant, Type B(144010)
Long QT Syndrome 1; LQT1(192500)
Long QT 2(152427)
Long QT Syndrome 3; LQT3 (603830)
Long QT 5(176261)
Long QT syndrome 6(603796)
Marfan Syndrome; MFS (154700)
Marfan Syndrome, Type II; MFS2 (154705)
Noonan Syndrome 1; NS1(163950)

Services were asked to estimate how many genetic tests they undertook each year. Out of a total of 1931 total tests (Table 5.6), 717 (37%) were performed for cardiomyopathy related diagnoses, 705 (37%) for arrhythmia disorders and 433 (22%) for Marfan and related conditions. It should be noted that, because specialist FH centres were not included in the survey, this will not include tests undertaken for mutations in FH genes.

Table 5.6 Total number of genetic tests carried out for each group of conditions

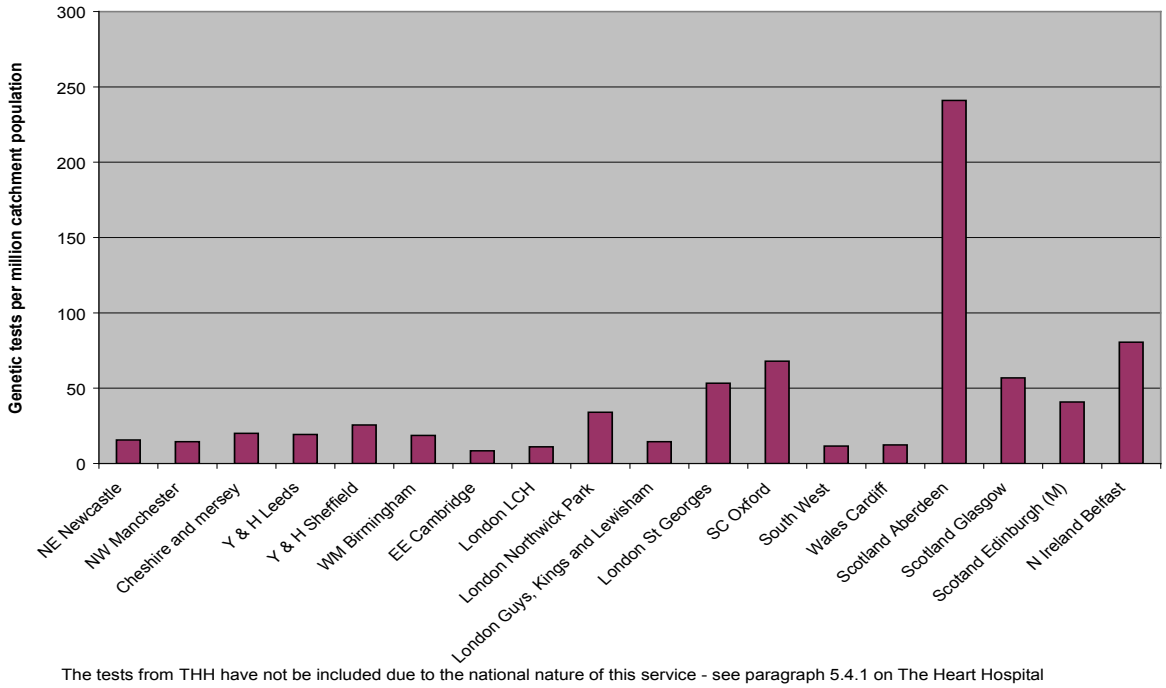
Condition	Total number of tests performed
HCM	464
DCM	115
Sarcomere proteins*	8
ARVC ARVD**	115
LQTS	656
Brugada	25
CPVT	24
Marfan/Fibrillin	431
Loeys Dietz	2
22q11 FISH***	15
Karyotype*	15
Other	61
Total	1931

* Relevant to the molecular diagnosis of inherited cardiomyopathy
** Classified as a cardiomyopathy
*** These are more general tests rather than specific cardiac related tests but may have been performed to diagnose a syndromic condition in the presence of cardiac abnormalities

5.6.1 Where were the tests carried out?

All centres carried out some genetic testing but the numbers of tests undertaken at each centre ranged from 21 (Eastern Region) to 238 (Oxford) for centres outside London. London centres carried out 689 (36%) of tests; almost half of these (306) were undertaken by THH. In relation to catchment population the number of tests carried out per million population varied considerably from 8.4 to 240 with a median of 19 (see figure 5.6). The number of genetic tests undertaken per total patients seen also varied widely from 1 in 24 patients to approximately 1 in 1 with a median of 1 in 4.6.

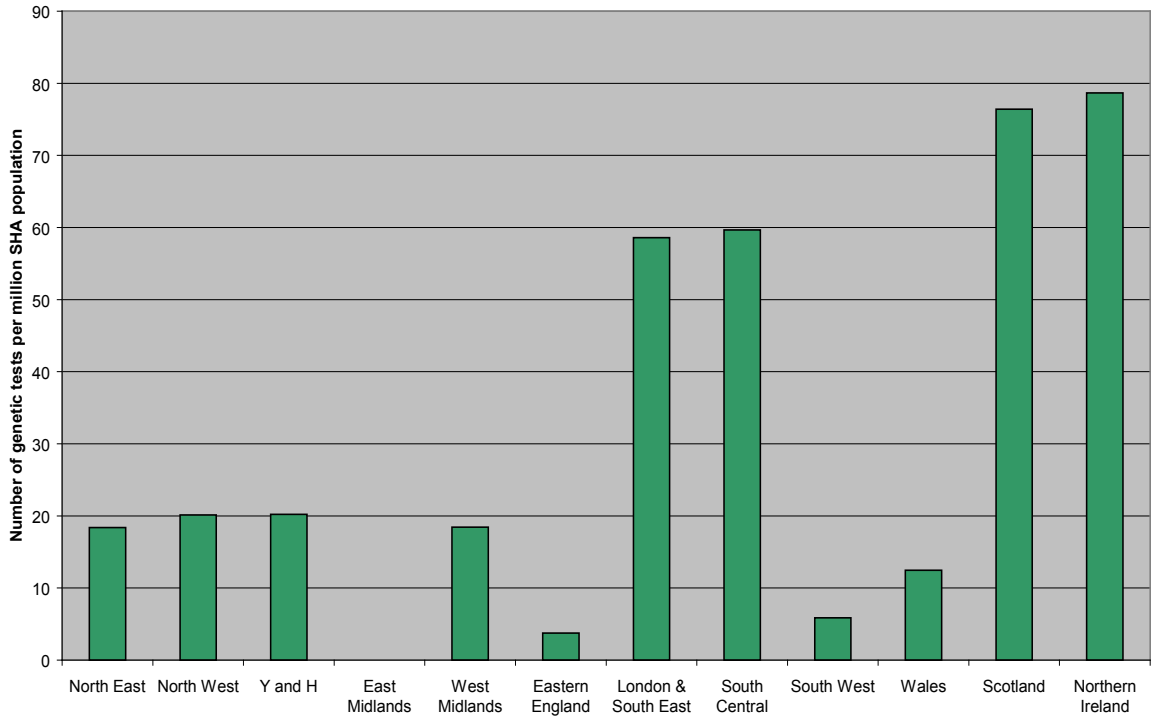
Figure 5.6 Number of genetic tests per million catchment population



The tests from THH have not be included due to the national nature of this service - see paragraph 5.4.1 on The Heart Hospital

This variability persists overall at SHA/regional level. Figure 5.7 shows that there is more than a 20 fold difference in the number of tests performed per million population from the most poorly served to the best served region.

Figure 5.7 Number of genetic tests per million SHA/regional population



5.7 Survey of FH services

Independently of this review, in 2008 HEART UK (Wierzbicki 2008) undertook a survey of the known 120 lipid clinics in a variety of settings. Responses were received from 67 clinics (56%). The clinics were asked about the numbers of patients seen including the numbers of children, arrangements for providing services for children with FH, the personnel involved in services, and the support required for cascade testing.

The numbers of FH patients seen by the services ranged from fewer than 50 to more than 300 representing 22% of all lipid clinic patients. Thus while there were a few clinics with large numbers of FH patients, most had few FH patients, raising the concern that these may not be cost effective with regard to specialised FH services such as for children or cascade testing. Most referrals were made by GPs (70%). Cardiology/chest pain clinics were the second most common source of referral with 8% of patients coming from this source.

Services for children with FH are significantly underdeveloped, with fewer than 600 children being seen UK wide compared to 14,000 children aged under 10 with FH from the 1:500 population prevalence. The survey also revealed that half of the services manage children in an adult lipid clinic, with only 20% of clinics caring for children in a specialist paediatric clinic despite NICE recommendations that children or young people with FH, or being investigated for FH, should be referred to an appropriate child-focused setting. A further 10% of clinics managed children in a general paediatrics setting.

Only 9% of clinics had access to a genetic nurse. About two thirds of clinics felt it would be very helpful to have a genetic nurse if genetic testing was available.

Services were asked if they audited whether target LDL levels were achieved after treatment – only a third of services do undertake such audits. The survey reported that almost a third of clinics currently discharge patients after lipid levels are stabilised. NICE recommends an annual review for every diagnosed FH patient, and while it may be feasible for this to be carried out in General Practice, currently over 67% of clinics reported that shared care arrangements with GPs have not been established. Treatment by apheresis was available in only 6 centres, with 34 patients across the UK identified as receiving this treatment.

5.8 Discussion and conclusions

Our survey presents a snapshot of services in early 2008. Although there are likely to have been some changes since then – for example in the appointment of new BHF-funded nurses – it is unlikely that the situation has improved significantly.

Although most regions have an ICC service, or a service is under development, the two main conclusions from our survey are that the capacity of services is inadequate to meet either current or future estimated needs, and that service provision is highly unequal across the country. Although we were not able to make an accurate calculation of the shortfall in provision, estimates based on extrapolation from current service provision suggest a shortfall of perhaps 7,000 new patients per year. Epidemiological data, indicating that prevalent cases of ICCs number in the hundreds of thousands, suggest that the shortfall may be significantly higher and that it will be likely to increase as more genetic tests become available and cascade testing gathers pace.

All the measures of activity used in our survey (for example, number of outpatient clinics, consultant sessions, total patients seen, new patients seen, or genetic tests carried out per million population) suggest significant inequity in service provision across the country, with typically 10- to 20-fold variation between the best and worst provision.

The number of new patients seen per million population is probably the key comparative indicator of level of service provision. This varied ten-fold between the most active and least active regions highlighting inequity in access to services.

Services are highly London-centred. 59% of outpatient clinics, staffed by 60% of the medical consultant sessions in the UK, take place in London, representing a six fold greater per capita level of service provision than the rest of the UK. While the London services cater for some patients referred from the regions, the numbers of such patients are not known for all London services and it is thought unlikely that London services are compensating significantly for lack of provision in the regions. With the exception of THH (and even for this service 57% of patients were referred from PCTs in London and the SE Coast Regions), most provision by the London services is likely to be for patients based in London and the neighbouring Regions.

Some caveats in the interpretation of our survey data should be noted. For example, variable (but generally small) numbers of patients with non-genetic conditions attended clinics held by some services and are counted within activity figures for those services. However, two-thirds of services are devoted exclusively to patients with ICCs. Conversely, responses from some services indicated that some patients with ICCs are being seen within normal genetics or cardiology clinics. While some of these patients' needs are being met, they will not be receiving the specialist multidisciplinary service that they require.

Discussion of the survey results within the Working Group suggested that some of the observed variation among services (for example, in numbers of outpatient clinics held) might be explained by differences in the way the survey questions were interpreted. We therefore asked all services to verify if sessions by professional staff in the clinical ICCs sessions they had told us about were for designated ICC clinics that were consultant led; the figures presented are the verified figures. In addition, services were asked if sessions by professional staff were specified 'in the job plan' ie. sessional commitments that are formally agreed. Of the 17 services that responded to the question, 10 said that the consultant sessions were in the job plans, 1 further service responded with an unsure 'yes', 5 services said that sessions were partly included in job plans and one service said that they were not in job plans. For genetic counsellor sessions, again, not all were included in job plans and not all were NHS funded. We conclude that, although it may not be justified to make detailed, quantitative comparisons based on our data, they represent a broadly accurate picture of current services and that our general conclusions are valid.

Like our survey, the HEART UK survey on FH services highlights great variation in provision and in particular a need to develop appropriate services for children. Services commented on a lack of genetic nurses; this deficiency is noteworthy in the light of the NICE guidance recommending cascade testing of relatives of patients with FH.

In summary, there is an urgent need to develop strategies to increase overall provision of ICC services and to ensure the most efficient configuration of clinical and laboratory services. Service provision needs to be increased across the UK including London.

Chapter 6 What makes a specialist service?

6.1 Introduction

An effective specialised service for ICCs must be capable of providing or organising care for the full range of these complex, variable conditions in a timely and integrated fashion. The ability to provide a comprehensive and effective service is grounded firstly in the individual expertise and experience of the various professionals involved in the service; secondly in their access to specialist investigations; thirdly, in their coming together as a multidisciplinary team; and finally in the effective working organisation of this team to deliver a highly specialised programme of care.

While some elements and functions of an ICC specialist service are unique to these conditions, there is also a set of generic features that any specialised service should demonstrate if it is to provide a tertiary resource for the population. Such features include robust commissioning, leadership, advocacy, monitoring and audit of quality standards and health outcomes, outreach through education and training, and ensuring equity of access.

Where possible, our discussion of the features that should characterise a successful specialised ICC service is accompanied by information, from our national survey, about the services that are currently available across the country.

6.2 Scope of the service

Ideally, a comprehensive ICC service should be responsible for ensuring provision of care across the full range of ICC conditions. This should include:

- cardiomyopathies
- arrhythmias
- multi-system disorders with significant cardiac manifestations
- aneurysmal disorders
- muscular dystrophies
- familial hypercholesterolaemia.

Where a particular condition is not covered by direct provision (for example FH) the ICC service should be clear what input it provides to care for these patients. This input might include, for example, support for cascade genetic testing or the provision of genetic advice. For certain conditions, such as muscular dystrophies and congenital heart disease, care will be provided in conjunction with other specialist services.

Box 6.1 Conditions covered by current services: findings from our survey

Most services described how they covered the clinical area with a variety of joint specialist clinics. For example, the West Midlands service described joint clinics for LQT, cardiomyopathy, GUCH, a 'multi-condition' clinic and Marfan, with plans to develop a joint paediatric arrhythmia clinic. However these joint specialist clinics were usually not brought together into a unified ICC service.

Whilst 94% of services provided care for people with arrhythmia/SCD and cardiomyopathies, and 88% provided a service for Marfan syndrome, only 24% covered aneurysmal disorders, 18% congenital heart disease, 24% inherited metabolic disorders and 24% lipid metabolism.

Our survey findings show that there is inadequate provision for some conditions within existing services. Where it is not possible to provide care for specific conditions within a particular service, clear arrangements must be made for care of these patients and their families through another specialised centre. For the rarest conditions, such shared arrangements may be the norm.

6.3 Specialised professional roles

Although many documents have listed the individuals that need to be involved in a specialised service for the diagnosis and management of ICCs, it can be hard to determine 'what makes them specialists', particularly as this is not an area in which there is formal sub-specialisation, or sub-specialty training. The Working Group sought to bring together the views of the various experts about their particular roles and expertise; their accounts are summarised here.

In our survey we asked services to provide information on the range of specialist roles that form part of their service. In this section we have also drawn in information, obtained from our survey, on the numbers of different specialist professionals and the balance of expertise in current services.

6.3.1 Consultant cardiologist

The role of the cardiologist is to make a clinical diagnosis and evaluation of the risk of sudden death. The emphasis is on cardiological assessment and in particular evaluation of the electrocardiogram, echocardiogram and other cardiological investigations. The complexity and variability of ICCs, and the difficulty of distinguishing them from a wide variety of other cardiac disease, mean that diagnosis and assessment require extensive training and experience.

Individual cardiologists in an ICC service may have sub-specialist expertise in areas such as paediatric cardiology (see below), electrophysiology or echocardiography. For example, the electrophysiologist will be expert in the use of anti-arrhythmic drugs, ablation of arrhythmias and the implantation of devices including resynchronisation therapy. The imaging specialist will lead in the analysis and interpretation of structural features when investigating the possibility of cardiomyopathy, using a range of techniques including echocardiography, nuclear medicine and cardiovascular magnetic resonance. Specialist follow-up of patients requiring monitoring may also be provided by the cardiologist.

The specialist cardiologist must have a sound understanding and appreciation of the role of genetics in key aspects of the diagnosis and management of ICCs. For inherited conditions where the heart is only part of a wider syndrome, specialist cardiologists are involved in clinical evaluation and provide advice on cardiac management to the clinical genetics team.

Finally the specialist cardiologist must have experience in dealing with bereaved families where genetic disorders are suspected, understand the importance of consent for tissue retention and management of samples, and work with coroners and pathologists in this context.

6.3.2 Paediatric cardiologist

Children referred to the cardiac genetic service represent a complex diagnostic, clinical and ethical challenge which differs significantly from that of the adult. Although many ICCs present in childhood or in early adult life, there is often an evolving phenotype and it may be difficult to make a definitive diagnosis until the child is fully grown. For example, HCM presenting in a young child is more commonly due to mitochondrial cytopathy than in an adult. Conversely, there are some cardiac genetic conditions (for example, Marfan syndrome) that have a specific infantile or paediatric form which differs significantly in prognosis, risk factors and treatment from the adult form of the condition. Expert assessment and age-specific management by a specialist paediatric cardiologist (taking into account both the physical and psychological maturity of the child) are essential.

The more general skills of the paediatrician are essential to the multidisciplinary team. These include, for example, liaison with community child health, education and social services, and the transition arrangements for the staged transfer of the older child/adolescent to the adult environment at an appropriate age. The paediatrician specialising in inherited cardiac disease also needs to be expert in issues of consent to testing and treatment of children.

6.3.3 Clinical geneticist

The geneticist's expertise is essential to refine the diagnosis of an ICC. In particular the clinical geneticist provides detailed examination of the family history with capacity to verify diagnoses through family and other records, experience in identifying dysmorphic features associated with rare genetic syndromes, and knowledge and experience in other rare disease areas such as metabolic or muscle disease that may have cardiac involvement. The clinical geneticist also has an understanding of the possible underlying molecular pathology of ICCs, likely clinical utility of testing, and interpretation of tests and uncertain results. Clinical geneticists have experience of providing advice to parents about recurrence, and counselling about possible prenatal testing. Systems for undertaking family follow up are well-developed within clinical genetics and include agreed professional practice over such aspects as how and when to follow up family members and what to do when problems arise.

Whereas some conditions and certain patients may be managed by a general geneticist within a general genetics setting, others will require a geneticist with particular experience in cardiovascular conditions and/or a specialist ICC setting where there is close working with the cardiologist with a special interest in genetics and the investigatory and support components of the multidisciplinary team.

Box 6.2 The balance between genetics and cardiology: findings from our survey

A total of 319 consultant sessions were assigned to 'genetics' or 'cardiology'. Of these, overall 93 (29%) were genetics and 226 (71%) cardiology. However, in London the service provision was much more dominated by cardiology (93% of sessions). In the rest of the UK, overall the services were dominated by geneticists (62% of sessions). However, again this was highly variable. Of the twelve services where figures were given, genetics provided up to 1/3 of the sessions for 3 services, between 1/3 and 2/3 for 5 services and more than 2/3 of the sessions for four services. It can thus be seen that the services do not all provide a balance of input between cardiology and genetics – most tend to be dominated by one specialism or the other.

6.3.4 Genetic counsellor

The genetic counsellor working within the ICC setting has generic roles, and may also have responsibilities specific to these conditions. Generic roles include taking the patient's family history and drawing up a detailed pedigree, eliciting patient's concerns and expectations, ensuring they understand the reason for referral, clarifying diagnostic information and providing counselling to enable informed patient choices. The genetic counsellor has responsibility for the development, maintenance and use of genetic registers and other records. He or she may order genetic and biochemical tests as clinically appropriate, liaising with laboratory colleagues over the likely utility of tests and discussing complex results that are difficult to interpret.

In the specific context of ICCs, the genetic counsellor needs good knowledge of the conditions in order to provide the necessary counselling, education and information support to patients. This specialist role may include providing advice on likely cardiac diagnostic and genetic diagnostic interventions; interpreting and communicating normal and abnormal genetic test results to patients; sourcing and interpreting information to enable calculation of recurrence risks and carrier risks; and identifying at-risk relatives and being able to advise them on appropriate ICC or genetic services.

Although a genetic counsellor may work mainly in the ICC service it is important that formal links with a clinical genetics department are retained in order to ensure clinical supervision and observation, opportunties to discuss cases with genetics colleagues and ongoing education.

Box 6.3 Genetic counsellors: findings from our survey

14 services employed genetic counsellors. The total WTE for genetic counsellors over the entire UK was 5.8, of which 33% was in London. The sessional input per month varied widely from 1 to 40 (for services outside London) with a median of 12.5 sessions.

6.3.5 Clinical laboratory scientist

The consultant or principal clinical scientist manages a team of junior clinical scientists and genetic technologists to provide a laboratory testing service, undertake translational research and implement new developments. Genetic testing for ICCs should only be undertaken in CPA accredited genetics laboratories where there is sufficient scientific, technological and clinical expertise to maintain the service at the forefront of developments.

The clinical scientist is responsible for reviewing the appropriateness of referrals against agreed criteria, either independently or in conjunction with clinical colleagues. He or she plans the most efficient and clinically appropriate testing strategy for each referral and must be familiar with the recommended laboratory methods and protocols. The clinical scientist is responsible for the correct interpretation of results, thus requiring extensive knowledge of the scientific literature and appropriate databases, and must provide clinically interpretive reports and further advice to the referring clinicians. He or she will recommend further investigations and indicate whether presymptomatic testing in unaffected relatives is available to the family.

6.3.6 Specialist cardiac genetics nurse

The specialist nurse provides emotional and psychological support to patients and families, along with accurate and easy to understand information about ICCs. The nurse acts as the identified contact for the family. This is of particular importance where a sudden death has occurred and the nurse is required to liaise with other family members undergoing clinical evaluation. The nurse also provides links, where appropriate, to specialist services in response to the individual and family needs. The BHF has currently funded a number of cardiac genetic nurse posts. Details of this initiative are included in chapter 3 in the ‘Other policy initiatives’ section.

Whilst the role requires a high degree of skill and liaison, the nurse also works autonomously and takes responsibility for the management of his/her own workload within the multidisciplinary team. The nurse organises specific investigations and particularly ensures the correct preparation and handling of blood samples for genetic analysis. The nurse also ensures accurate data are collected for case report forms. The nurse’s role also contributes to raising awareness of academic/clinical research within the clinical setting.

Box 6.4 Specialist cardiac genetic nurses: findings from our survey

10 services employed a specialist cardiac genetics nurse, amounting to a total of 8.5 WTE (53% in London). The five services outside London employed from 4–60 sessions per month with average of 32 and median of 28.

6.3.7 Cardiac physiologists

Non-physician cardiac physiologists, with training in areas such as echocardiography, electrophysiology or exercise testing, work with the consultant cardiologist in the diagnosis and management of patients. Specific training and expertise are required to recognise and interpret the complex and heterogeneous heart abnormalities in ICCs. The level of contribution of the cardiac physiologist to the diagnostic process varies depending on his or her knowledge and experience. Many of the services we surveyed reported that their multidisciplinary teams included cardiac physiologists with expertise in echocardiography and electrophysiology. In some centres, additional technical staff assist in carrying out these investigations.

6.3.8 Pathologist

Autopsies are undertaken by pathologists to establish a cause of death. In some circumstances it is not possible on initial investigation to establish a cause of death; where appropriate under these circumstances, the heart may be retained following discussion with the coroner for further detailed examination. These hearts are referred to specialist cardiac pathologists within the UK with an interest in SCD. Whenever possible the whole heart is received by the cardiac pathologist, but sometimes this is restricted to just samples of tissue blocks. A careful examination is undertaken of all the component parts of the heart, in particular the valves, the muscle and the coronary arteries, and blocks of tissue are taken for microscopic examination to look for abnormalities. Where appropriate additional samples are taken for genetic analysis where a particular ICC is considered. In many cases in spite of a detailed examination no specific diagnosis is reached. Nonetheless, the cardiac pathologist has an important role in defining any morphological abnormalities within the heart, guiding further investigations particularly in the area of genetic abnormalities and ensuring, with the appropriate permission, a repository of relevant tissues for further studies in the future.

6.4 Access to other specialist services

Many ICCs are systemic disorders, which means that patients may need diagnosis and management from a wide range of other services. For example, in Marfan syndrome involvement will be required from ophthalmologist and rheumatologist and, again, these specialists need experience in managing these rare conditions. Other conditions arise from inherited metabolic disorders - for these the identification of underlying disorders and the management of these and other system effects must be managed by experienced specialists. It is vital, therefore, that specialist ICC services build the necessary links with related specialties, including formalised care pathways, so that patients can be referred and care can be coordinated in the most effective and holistic way.

6.5 Access to specialist investigations

6.5.1 Cardiological investigations

The ‘Blueprint’ document notes requirements for a range of specialist investigations, technologies and equipment. In addition to these, specific types of investigations are needed for some ICCs such as Marfan syndrome, where ophthalmological and orthopaedic investigation is an important part of diagnosis and monitoring of the condition.

Echocardiography and other imaging technologies

The echocardiogram has an important role in the diagnosis of cardiomyopathies and in ruling out heart muscle disease in families with a history of sudden unexplained cardiac death. Specific protocols are required for some ICCs, and in some cases more advanced imaging technologies such as contrast echocardiography and tissue Doppler imaging may be necessary.

The information obtained not only confirms a diagnosis, but may also provide prognostic data. Dynamic echocardiography during exercise, or less commonly pharmacological testing, can be helpful in the assessment of symptoms (for example in patients with obstructive hypertrophic cardiomyopathy).

Other imaging technologies include cardiovascular magnetic resonance. Accurate assessment is made of biventricular dimensions and function as well as excluding a range of structural and tissue abnormalities. Findings complement the clinical and genotype evaluation.

Specialist electrocardiophysiological investigations

Equipment and resources are required for specialist ECGs including signal-averaged ECGs, ambulatory electrocardiographic monitoring and exercise testing (see below). Facilities are also needed for non-invasive or minimally invasive electrophysiology investigation including, for example, ajmaline provocation testing.

Exercise testing

Exercise testing, for example by conventional treadmill or upright bicycle ergometry, is an important component of diagnosis and risk evaluation. It also provides important prognostic information that is used to make decisions on prophylactic implantation of ICDs.

In some specialist centres, exercise testing is combined with respiratory gas analysis in order to obtain information on the physiological response to exercise. This can be helpful in detecting rare causes of cardiomyopathy such as respiratory chain diseases and may also be useful in differentiating athletic adaptation from pathological remodelling of the heart.

6.5.2 Findings from our survey

Nearly all centres had access on site to echocardiography and ECG, although for 2 services echocardiography had to be pre-booked. One centre did not have access to either facility and a further service had access only to ECG. A third service which was the part of an ICC service that dealt with Marfan syndrome did not have access to either facility for its Marfan clinic but its other ICC clinic had access to both echocardiography and ECG.

Ophthalmological testing for Marfan syndrome patients was only available at the time of the clinic for 1 out of the 5 Marfan services. The other Marfan services had to refer patients to a separate ophthalmology clinic or a service in a different hospital. 3 of the other services that were not specifically Marfan clinics had access to ophthalmological testing.

The other special investigations listed by services include: cardiac MRI and a full range of non-invasive and invasive investigations (Sheffield); exercise tolerance testing (ETT), cardiac MRI and drug provocation testing (St Bartholomew's Hospital/London Chest Hospital); tilt test, 24 hour monitoring and treadmill test and cardiac MRI (London Northwick Park); holter monitoring, ETT, cardiac MRI and ajmaline test (King's and Lewisham Hospitals); exercise ECG, signal averaged ECG (SAECG) and ajmaline test (London St Georges); cardiopulmonary exercise testing and SAECG (The Heart Hospital); cardiac MRI, spinal MRI, exercise testing, SAECG and provocation testing (Aberdeen) and max oxygen uptake (Glasgow).

Nine of the services commented on gaps in their services. The most commonly noted gap was access to echocardiography, highlighted by 3 services. Each of the other gaps was mentioned by one service: ready access to MRI, adrenaline testing, access to paediatric cardiology on site, multidisciplinary clinics, database and robust audit tools, and personnel for streamlining tests and the patient pathway. One service had addressed the issue of how to work as effectively as possible while integrating care

across disciplines: '*We feel that we have all the necessary investigations on site in clinic. This allows a one stop clinic approach. We try to avoid as much as possible experts sitting in one another's clinics. The appointment of a clinic coordinator with expertise in genetics and cardiology to oversee the most appropriate use of services and personnel has been of great benefit. We triage the referrals to the clinic and have a weekly meeting before the clinic for this.*'

6.5.3 Access to genetic testing

As discussed in Chapter 2, genetic tests are increasingly important in both the accurate diagnosis and the appropriate management of ICCs. They can aid diagnosis when other clinical tests such as ECGs are not adequately sensitive in detecting the presence of a disorder in all individuals. In families where there is a known mutation they can identify which individuals are at risk and which asymptomatic individuals can be excluded from further monitoring because they do not carry the particular mutation. In some cases, genetic tests can also enhance risk stratification and guide choice of therapy by enabling classification of the condition into one of the known genetic subtypes.

Our survey shows great variation in the use of genetic tests between different services, reflecting, at least to some extent, differences in the availability of and funding for genetic tests in different geographic areas.

6.6 Specialist non-clinical elements

6.6.1 Bereavement and counselling services

Finding out about ICCs and the experience of SCD in the family are likely to produce extreme levels of anxiety, stress and emotional turmoil at a time when decisions need to be taken about the best means of management for those who are affected, or might be at risk. The availability of therapeutic and bereavement counselling to assist people through these processes is an important part of the clinical service. One service provided a fulltime counsellor, whose role is described further in Box 6.5.

Box 6.5 A service with a bereavement and therapeutic counsellor: findings from our survey

The role of the counsellor is to offer 'emotional support in a safe and confidential environment where an individual can talk in depth about how they are affected by bereavement, the screening process or their diagnosis'. Typical issues for which counselling might be beneficial include survivor guilt, grief, fear, anxiety, depression, uncertainty of diagnosis, anger at misdiagnosis, family relationships, lifestyle changes and overprotection of children, financial, insurance or employment considerations. By working with individuals and families an appropriate package of care and support is developed. This may involve assessment, one to one counselling sessions, telephone support or referral to an appropriate agency near to where they live. Support is also available for those already diagnosed with an ICC.

(Regional ICC Service based in Leeds)

6.6.2 Voluntary organisations

Many patients and families gain valuable practical and emotional support from patient support groups. In some cases these services act as a point of initial contact through which families find out about the specialist cardiac services. In other cases they provide ongoing information and support. Our survey findings indicate that most services do usually tell patients about support groups; those mentioned

included SADS UK, Arrhythmia Alliance, CMA, CRY, Marfan Association and the BHF. Some services also used patient information developed by these organisations.

6.7 The specialist multidisciplinary team

Key to the provision of a specialist service is a strong multidisciplinary team (MDT) that includes, or has access to, all the professional roles and specialist resources described above. The ICC service should be provided in a way that brings together the main cardiac elements and genetic elements as equal partners.

The MDT as a whole should have responsibility for the following functions in the care of patients:

- receiving referrals
- provision of advice about possible referrals
- diagnosis and assessment
- treatment or advising on treatment
- input to specialist care provided by other specialties (for example inherited metabolic disease, ophthalmology, specialist clinics such as Marfan clinics)
- input to long term monitoring and surveillance and care including shared care arrangements with other hospitals and support provided by voluntary organisations
- identification of family members at risk and ensuring appropriate evaluation
- discharge
- prioritisation of services for patients, such as access to genetic testing, according to clinical need.

Our survey findings (Chapter 5) show that, in current services, a range of specialised professionals does usually contribute to care, but that many teams are incomplete. The relative weight given to different areas of specialist expertise is variable (see Box 6.2), and formalised arrangements for the MDT are often not in place.

Box 6.6 The multidisciplinary team: findings from our survey

Although most services operated in a multidisciplinary fashion, most did not describe a formal multidisciplinary team with agreed leadership and membership. It was usually not clear how the various specialists worked together to meet the complex needs of patients at various stages of diagnosis, management and cascading to the wider family. For many services the genetics and cardiac elements were operating in parallel. In some services the genetic element of the ICC clinics was provided by a genetic counsellor rather than by a consultant clinical geneticist.

Three services (Leeds service, Sheffield service and THH) did give details of MDT membership and operation (see service overviews, Chapter 5).

It was usually not clear how the various specialists worked together to meet the complex needs of patients at various stages of diagnosis, management and cascading to the wider family. The Leeds service described '*clinical meetings of the MDT prior to each clinic to discuss cases*' and the appointment of a clinic coordinator to make multidisciplinary working as efficient as possible. The Sheffield service described 'regular' MDT meetings and the Oxford service described monthly MDT and weekly laboratory liaison meeting.

6.8 The ICC specialised service in action

The setting up of a specialist service requires more than simply a collection of experts from different disciplines. Rather, it must be a resource which ensures that, as far as possible, the needs of the whole population with regard to ICCs are met and that patients and families are managed in a holistic way that ensures the most effective and efficient use of resources.

Our survey of current services highlighted several areas of practice where there was variation across the country. These included mechanisms for ensuring appropriate referral, availability and use of genetic testing, cascade testing in extended families, overall structural organisation, commissioning arrangements, relationship with cardiac networks, ensuring equity of access, and formulation and monitoring of quality standards. Several services pointed out gaps in their provision, and areas in which they would like to make improvements, but the survey also revealed examples of good practice that could be extended more widely.

6.9 Ensuring appropriate referral

6.9.1 Raising awareness and outreach

As a centralised, specialist service, the ICC service must find ways of ensuring that there are effective referral pathways and processes from the whole of its catchment population. Achieving this goal requires an awareness of the service, and recognition of patients and family members for whom referral is appropriate, by all those who are the initial point of contact.

Services currently recognise deficiencies in referrals: "*We are aware that across the region our referrals are patchy and there are many more patients who would benefit from our service than are currently being referred. We are aware of many index cases (in other hospitals and primary care) that have been offered no formal family review*".

Referral to the specialist ICC service may be initiated either through clinical channels or, in the case of a sudden unexplained death, by the coronial service (Box 6.7) or through voluntary organisations representing patients and families. Close working relationships are needed with these non-clinical organisations and services, both to ensure that families are referred appropriately and that they receive ongoing emotional and practical help. One service mentioned "*a pressing need to improve detection and management by raising awareness and provision of education. This applies to hospital doctors, primary care, nurses, coroners, professions allied to medicine and the public at large*."

It is important that coroners should be aware of the possibility that an unexplained death, particularly of a young person, could be due to an ICC, and initiate the appropriate specialist investigations. As discussed in Chapter 3, a newly established Coroners and Pathologists Special Interest Group is working to provide guidance to coroners and pathologists dealing with cases of SCD and improve awareness of ICCs.

Box 6.7 Coronial services

A coroner is an independent judicial officer appointed to a specific area. He/she is required to make inquiries (and, if need be, conduct inquests) on those reported to him whose bodies are (physically) lying in his district and where he/she has reason to suspect that the death was due to violence, was unnatural or sudden of unknown cause.

If the coroner decides on the information before him that the body should be subject to a specialist test or examination (normally, this would take the form of histology, toxicology, specialist cardiac pathology etc) to determine the cause of death then he may direct that such a 'special' examination be made. This cannot be primarily undertaken for the benefit of other family members but only for the purpose of refining or determining the cause of death. If, however, such a test were to demonstrate a genetic condition then the results of these tests could be made available for the treatment of family members.

6.9.2 Referral guidelines

Services need clear referral guidelines and agreed patient pathways for patients with suspected ICCs. These should build on the ways in which patients are likely to present to primary care or district cardiology services and should give clear criteria to aid decision making. Criteria may need to include such aspects as what strength of family history is required (for example number of first degree relatives affected), age of onset for conditions such as HCM that might increase the likelihood of inherited disease, and how a sudden unexplained death would be defined (eg age under 40 years).

Guidelines should also provide the necessary filters to ensure that the specialist service is not over-burdened. (For example the Northern Genetics service suggests that patients with late onset HCM or DCM over age 30 should be referred for further risk stratification to the cardiology clinic). The guidelines should, in addition, set out the preliminary clinical work-up that should have been carried out. For example the Northern Genetics service requests that for Marfan patient referrals there should be an echo report and ophthalmological assessment.

Services also need to decide and demonstrate:

- who the guidelines should be available to (geographical region, service group, public?)
- how the guidelines will be made accessible (for example via website) and publicised
- how referrals should be made
- any arrangements or plans for auditing awareness, use and effectiveness of guidelines
- arrangements for auditing referral patterns including variations by condition, referral source, geography and other factors such as ethnicity or social class.

The only service that provided us with a copy of their referral guidelines (which they described as 'network ratified') and agreed patient pathway was the Northern Genetics service (CARDIGEN) see Box 6.8 (available from Dr Paul Brennan at the Northern Genetics Service).

Box 6.8 Referral guidelines: example from our survey

The Northern Genetics Service and CARDIGEN (the cardiac networks for the Northern and Coast to Coast areas) have produced a 26 page document on referral and management guidelines.The document contains referrals guidelines on:

1) Inherited cardiovascular connective tissue disease
   - suspected Marfan syndrome/inherited predisposition to thoracic aortic aneurysm/ dissection
   - suspected cardiovascular collagen disorder.

2) Familial cardiomyopathy (HCM, DCM, ARVC)
   - people with diagnosed cardiomyopathy
   - people with a family history of cardiomyopathy.

3) Familial arrhythmia (LQTS, Brugada, SQTS, FAF, CPVT)
   - people with a clear diagnosis of 'genetic arrhythmia'
   - people at 50% risk of an inherited arrhythmia syndrome (confirmed family history)
   - people with suspected genetic arrhythmia and no family history.

4) Sudden unexplained death and sudden cardiac death
   - pathology pathway
   - clinical pathway for relatives.

Working relationships are required with the various specialist services that might need to refer patients and to whom patients might be referred for specialist aspects of management. As well as obvious sources for referral from cardiology, primary care and paediatrics, close relationships for referral variously mentioned by the services that responded to our survey included rheumatology, cardiothoracic surgery, clinical biochemistry, emergency medicine, neurology, ophthalmology, orthopaedics, dermatology, sports medicine, pathology, neuromuscular clinics and gynaecology.

6.10 Diagnosis and management of patients and their families

The ICC service needs to demonstrate that it has procedures in place for specialist investigation and management of patients, and for identification and follow-up of at-risk family members. As well as the expertise of the individuals involved in the multidisciplinary team, this should also involve the use of explicit diagnostic and clinical protocols.

6.10.1 Protocols and guidelines

The main guidelines that are in use are:

- Clinical indications for genetic testing in Familial Sudden Cardiac Death Syndromes: an HRUK position statement (Garratt 2008)
- The American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (Zipes DP 2006)
- Guidelines produced by the Task Force of the European Society for Cardiology on Sudden Cardiac Death (Priori 2001)
- The Ghent criteria for the diagnosis of Marfan syndrome (De Paepe 1996)
- Guidelines supporting chapter 8 on the Department of Health website (includes implementation

documents on Wolff-Parkinson White syndrome, Acquired LQT syndrome, Brugada syndrome, congenital LQT syndrome, HCM and ARVC) (Department of Health 2005)
http://www.dh.gov.uk/en/Healthcare/NationalServiceFrameworks/Coronaryheartdisease

In addition a number of other locally produced guidelines were used by services.

Box 6.9 Management guidelines and protocols: findings from our survey

When asked whether they had agreed management protocols, most services responded that they followed professionally accepted management guidelines for some aspect of their service. Some were in the process of developing locally agreed guidelines within their own network. The broad range of replies is given below:

- CARDIGEN guidelines used.
- the Cheshire and Mersey Cardiac Network are developing management guidelines and a draft was attached.
- other services noted that the GHENT diagnostic criteria are used which may involve referral to a cardiologist, ophthalmologist and radiologist. Guidelines for HCM and DCM were also in use.
- the protocol published by the Rotterdam group was mentioned by a service.
- flowcharts for investigations were received from St George's Hospital and THH.
- THH also noted the following management process: pre-screen pedigree analysis to ECG/ Echo/CPEX/SAECG to Nurse specialist to Consultant to DNA blood test/family screening/ICD counselling/surgery.
- one service noted that they used management guidelines for adult arrhythmias but not for other conditions.
- other services commented that only a few guidelines are in use but that most are in a development stage and are not formalised.

6.10.2 Methods for assessing risk

Services were asked to describe how an overall assessment of risk is made and how this is communicated to patients. It is recognised that this is a complex process and is hard to sum up briefly but the following illustrations in Box 6.10 provide some examples of how risk assessment is achieved.

Box 6.10 Methods for assessing risk: findings from our survey

Most services used a combination of genetic and cardiological assessment to provide an overall risk, although only one service (London Chest Hospital) provided an overall annual risk assessment for sudden cardiac death.

Three examples of approaches to risk assessment are given below.

ICC Risk Assessment Protocol

1) What is the referring cardiac diagnosis/family history?

2) What is the medical/cardiac history of the patient consulting? What is their age?

3) Appropriate cardiac investigations are performed. If there is a clinically useful genetic test available only a basic ECG might be requested whilst genetic counselling and diagnostic / predictive testing are offered.

4) A multidisciplinary (cardiology + genetics) team meets to review 1) – 3) and decides what other investigation / management is needed. This might include exercise testing, continuing cardiac surveillance, provocation testing, long-term arrhythmia monitoring or treatment with ß-blockers or an ICD(Cheshire and Mersey).

Risk assessment methodology is condition-specific. Assessment of inheritability risk is determined via mode of inheritance (commonly autosomal dominant giving 50% risk to children) and detailed assessment of individual family pedigrees working together through the MDT. Individuals affected by any particular condition will then undergo further evaluation to determine their individual risk from the condition, for example HCM patients are assessed specifically for a family history of premature sudden death due to HCM, unexplained syncope, non-sustained VT on holter monitoring, BP responses to exercise testing and the degree of LV hypertrophy. Similar algorithms are followed for other conditions (Sheffield).

Clinical assessment in the Heart Muscle clinic includes an annual estimation of mortality from sudden death/stroke. These risks are communicated in terms of relatively high risk (action advised), moderate risk (enhanced surveillance advised plus in depth discussion of risk/benefit of intervention) or low risk (routine annual assessment). Symptom status is also assessed annually where indications for intervention are discussed accordingly. Heredity is discussed by the cardiologists and by the clinical geneticists. Autosomal dominance and incomplete penetrance are introduced as important concepts. The limitations in the ability of genetic testing to provide a diagnosis are discussed, as is the limited clinical utility (with respect to prognosis) of such a diagnosis when made.

In the Inherited & Congenital Arrhythmia Clinic, risk assessment for patients with inherited arrhythmia syndromes is based on clinical phenotype and all recognised parameters published in the medical literature, for example QT interval in Long QT syndrome and symptoms in Brugada syndrome. The importance of cascade screening, modes of inheritance and clinical manifestations of the disease are discussed carefully with patients during consultations, as are the relative risks and benefits of different management strategies. Clinical status is regularly reviewed and patients are advised about lifestyle modifications (for example medication avoidance in long QT) and strongly encouraged to contact the hospital immediately in the event of new symptoms (London Chest Hospital).

6.10.3 Patient information

Many voluntary organisations have produced patient information in the form of leaflets, booklets and CDs. Much of this information is also available electronically. The following list is not exhaustive but provides information on the range of materials available. The CMA has produced a series of CDs on cardiomyopathy as well as booklets on HCM, DCM and ARVC. CRY has produced a booklet on SCD in young people. The Marfan Association has produced booklets with the BHF on Marfan syndrome and a number of leaflets on aspects of living with the condition such as pregnancy in Marfan syndrome and a booklet for teenagers. SADS UK has produced leaflets on LQT, Brugada syndrome and CPVT. Other organisations such as the Arrhythmia Alliance and BHF have also produced patient education materials. These were the sources of information services reported using.

Box 6.11 Agreeing genetic tests: findings from our survey

Services were asked how genetic tests were agreed and, in particular, which individual or department acts as gatekeeper for the test. They were allowed to tick more than one box, on the basis that there might be more than one mechanism for agreeing tests. 20 services answered this question. In all services, except the Heart Hospital, a consultant geneticist was involved in agreeing tests. Other contributors to decision making included a multidisciplinary team (7), the genetic laboratory (5), agreement by laboratory on fulfilment of agreed criteria (4), the specialist cardiology department (4) and the involvement of the PCT (2).

All but 1 service rated criteria that were important for the agreement of tests for individual patients. Ranking of first, second and third was awarded 3, 2 and 1 points respectively. The most important criterion was estimated clinical utility (44 points), followed by fulfilment of formal criteria (22 points), and cost (13 points). Integration of the test in an agreed care pathway (11 points) and availability as a UKGTN test (9 points) were also important factors.

6.10.4 Management of children

Particular care is needed in the management of children in families affected by ICCs. For many of these conditions, the natural history of the condition is unknown. If genetic testing in a child reveals a pathogenic mutation it may be difficult to predict the likely age of onset of symptoms or their severity. Ethical issues raised by genetic testing in children are discussed further in Chapter 7.

For some ICCs, evidence is accumulating which suggests that early initiation of treatment may be beneficial even in the absence of overt symptoms of disease (see Box 2.2 and Box 7.2). It is important that ICC services should be equipped to manage children in an appropriate setting that will usually include separate facilities and specialist paediatric staff. Our survey did not address this issue but the HEART UK survey on FH highlighted lack of dedicated facilities for children as an area of major concern (see Chapter 5). ICC services should have the whole family as the focus of care – a model more familiar to genetics services than to cardiology. Genetics services may be able to provide guidance to cardiology services in developing this model of service provision. Working Group members also reported problems at the time of transition between paediatric and adult services. Guidance on transition for children with long-term medical problems is included in *Transition: getting it right for young people: Improving the transition of young people with long term conditions* (Department of Health 2006).

6.10.5 Managing risk in families: cascade testing

An extra dimension is introduced to the ICC specialist service by the need to cascade specialist investigations through the extended family of the index case. Though simple in concept, the cascade system requires careful design and evaluation. For example, it needs to enable coordination of testing for a whole family by different health professionals in different geographic locations, to manage and record the different levels of consent that individuals and families have given and to provide information on the precise clinical and/or genetic abnormalities to enable testing. For this reason, the programme is unlikely to succeed unless there is an organised system for family record keeping, specialist services that are accessible to the various branches of the family, and an adequate IT infrastructure.

Our survey findings (see Box 6.12) suggest that, in practice, although the methods and mechanisms of cascade testing are firmly established within clinical genetics, they are less familiar within cardiology and, indeed, that cascade testing is not always a routine part of family management.

Box 6.12 Cascade testing: findings from our survey

Services were asked what pathways they had for cascading diagnostic information in the family and for follow up either in their own or another NHS service. Replies were received from 19 services. Most services (11 of the 20 services) do cascade through the family. Only 1 service specifically noted they had no mechanisms for cascading information. The information provided by the remaining services was not clear enough to judge whether the index patient was the main means of cascading information to other family members.

Mechanisms included:

- informing patients which of their relatives would be eligible for testing
- asking patients to contact relatives for referral to the service
- giving out 'to whom it may concern' letters
- with patient's permission contacting GP/cardiologist
- contacting relatives by post with permission from proband.

Although some form of cascade testing is generally in place, it is evident that there is no nationally agreed method or mechanism and that the process is not formalised. Some services quoted 'routine genetic pathways', 'routine clinical methods', and the leadership of the clinical genetics service or role of the genetic counsellor in initiating and undertaking family investigations ('not formalised but well organised through the genetic services' (Scotland Glasgow).

However, services noted as gaps:

- lack of a formal structure for conducting family studies (London LCH)
- 'insufficient genetic counselling/support staff to undertake cascade family screening in a timely manner (Scotland Grampian).

Additional points noted in the survey replies included:

- one service has a follow up system to check that at-risk relatives in their region have made contact
- one service has 'lesion specific' information sheets that can be given to relatives
- one service uses the pre-clinic nurse to try to achieve referral for the whole family
- one service commented that it spends a great deal of time working with other organisations such as primary care, coroners and other hospitals to obtain and distribute information to the families.

Within the area of ICC, services for FH are leading the way in developing cascade systems, based on a similar programme that has been active in the Netherlands for many years (Box 6.13). Such work may provide a valuable prototype for a cascade approach in other genetic conditions, including other ICCs. Initial health-economic research on cascade testing suggests that the approach is cost-effective.

Box 6.13 Cascade testing pilot using Netherlands methods

The Wales Familial Hypercholesterolaemia Project (WFHP) is undertaking a pilot test of databases to support family cascade testing. One database, The Pass Clinical database application, is just completing a 3 month pilot. A Dutch organisation, StOEH (Dutch National screening programme for FH), has used the Pass Clinical database to coordinate their cascade testing and has diagnosed over 13,000 individuals with FH in the Netherlands.

The application has several features that make it well suited to support the WFHP:

- integrated workflow management allows the steps in the cascade testing process to be standardised and controlled with all the relevant specialists having access
- integrated reporting and digital archiving
- integrated pedigree drawing
- flexible data collection.
- transfer of individuals to allow the follow up of certain individuals in a family by colleagues (for example in a different geographic location)
- paperwork and consent management.

Box 6.14 Health economic analysis of cascade testing

A cost-effectiveness analysis for HCM showed that the incremental cost per life year saved was £12,264 for the cascade genetic compared to the cascade clinical approach. Genetic diagnosis is more likely to be cost-effective than clinical tests alone. The costs for cascade molecular genetic testing were slightly higher than clinical testing in the short run, but this was largely because the genetic approach is more effective and identifies more individuals at risk. (Wordsworth *et al.*, DNA Testing For Hypertrophic Cardiomyopathy: A Cost-Effectiveness Model unpublished data from Oxford Genetics Knowledge Park Study).

The London IDEAS FH cascade audit project examined the cost of finding and testing one relative. The average cost was £500 (with a range of £330-£2,470 between clinics). Based on their findings and the national FH screening programme in the Netherlands, they concluded that cascade testing for FH was highly cost-effective, with an estimated cost of US$8,700 per life year gained (discounted) and so well below the £20,000 per QUALY used by NICE as a benchmark for cost-effectiveness (Hadfield 2007).

As the cascade approach becomes part of the standard of care for a number of genetic conditions, there is a need to set standards and develop mechanisms to ensure that it is done effectively. Elements that need to be considered include:

- how and by whom the decision to cascade is taken
- who is responsible for undertaking cascade testing
- how relatives in different geographic regions will be managed
- what mechanisms are needed when the cascaded information is a genetic abnormality and when it is based only on clinical assessment

- what supporting organisational structures are needed (for example family records, databases of genetic findings, methods for recording consent)
- how care and management of the whole family will be coordinated
- how to ensure that relatives have received information
- how the process can be encouraged/expedited (eg collections of good practice, standard letters of invitation, consent forms, standardised condition-specific information, education of other professionals)
- how the process will be audited.

Support is needed from specialist genetics services, particularly during developmental phases to help set up protocols, to provide educational support in working with families based on sound clinical and ethical principles, and to supervise the management of families where there are difficult issues such as family breakdown or adoption.

6.11 Effective structural models for an ICC service

The ICC service should be available and accessible to all its catchment population. Whilst it is usually necessary that it should be sited geographically in a major tertiary centre (often where there is a regional genetics service) the service must find means to reach out to its feeder health and other services to ensure that individuals with ICCs are diagnosed and managed effectively.

Our survey revealed a number of models for ensuring that the service was provided across a whole population (Boxes 6.15 and 6.16). Successful models included a 'hub and spoke' model in which tertiary activities were concentrated in one or a small number of central facilities, with less specialist aspects of care devolved to district cardiology services; and models involving development of 'satellite' specialised clinics, sometimes in order to provide care in more remote areas.

Box 6.15 Specialist centre with satellites

Some services have established peripheral clinics; for example, the Leeds service has established a further clinic at York District Hospital and is in the process of establishing a paediatric/genetic clinic based at Hull Royal Infirmary.

The Cardiff service plans to develop satellite clinics to service other areas in Wales. The Heart Hospital (London) has telemedicine links with Glasgow and Belfast.

Box 6.16 Hub and spoke model

Within the North of England Cardiovascular Network we employ a 'hub and spoke' approach to assessment and surveillance which acknowledges the limited availability of specialist clinical expertise around inherited cardiac conditions and the important role of district hospitals in on-going patient care. Tertiary ('hub') services – including specialist cardiac genetics clinics and specialist cardiology services – are concentrated in teaching hospitals in Newcastle upon Tyne and Middlesbrough. Essentially this creates a network in which patient pathways are clearly stated, clinical management becomes standardised and work is devolved to an appropriate level within the network.

An example of the system in operation

A patient with a family history of HCM is referred to the Northern Genetics Service by her GP. The patient is seen in a 'hub' cardiac genetics clinic by a consultant in clinical genetics, where genetic testing and cascade family screening are discussed. In that clinic she also has an echo and ECG, which are seen by a cardiologist and considered normal. Genetic testing is not possible in this particular family because the two known affected relatives are deceased. Cascade screening using echo and ECG is therefore offered to all at-risk relatives identified from the family tree. This work is undertaken at 'spoke' district cardiology units local to the relatives, according to a network guideline. The patient's sister is diagnosed with HCM as part of this process and is referred to the 'hub' for advice about management of her HCM and the applicability of genetic testing. Her ongoing cardiology care remains with her local 'spoke' cardiology service unless she needs more specialist intervention. Her genetics consultation takes place in a 'hub' cardiac genetics clinic. Following the identification of a gene mutation in her, cascade genetic testing is offered to at-risk relatives, coordinated by a genetic counsellor. Individuals identified as mutation carriers are offered cardiology assessment and on-going surveillance in a 'spoke' unit according to network guidelines, and are referred to the 'hub' if their local cardiologist needs advice on their management.

Following initial expert diagnosis, assessment and provision of advice on best management, many patients and families will be able to be followed up in less specialised district cardiology services, which may have the advantage of being closer to home. However, appropriate arrangements will need to be made to ensure that the services to which care is devolved have the necessary expertise and equipment, understand clearly their roles, and know when and how to refer back for further advice.

Box 6.17 Follow up and shared care: findings from our survey

It was apparent from our survey that most services do not have formalised arrangements for follow-up, either in general or with respect to individual patients.

One example of follow-up arrangements was provided by the Northern Genetics Service, which had explicit arrangements with district cardiology services in which there were local leads for inherited cardiovascular disease for ongoing management of patients. In particular, in this service cascade surveillance for family members was devolved to district units.

The Leeds service noted that '*where possible we refer patients to local paediatric cardiology for follow up and adults are followed up where possible within the Regional Cardiac Network*'.

6.12 Commissioning the ICC specialist service

The complementary roles of commissioners and cardiac network managers are critical to the provision of high quality, secure and stable services to a population. Our survey findings (Box 6.18) indicate that most current services have not been established formally as specialised ICC services operating within the cardiac network and so have not been formally commissioned.

Box 6.18 Commissioning of ICC services: findings from our survey

Although most services were provided from Regional Genetics services only two services (Northern Genetics and South Yorkshire 'regional IHD service') explicitly stated that the inherited cardiac disease service was commissioned as a regional service as part of the cardiac network provision.

Outside London four services (Northern Genetics, Leeds, Sheffield and Oxford) described themselves formally as a cardiovascular genetics service. Most services, however, were not formally constituted as ICC services but had grown as joint genetics/cardiology services in response to increasing levels of referrals and recent DH initiatives around sudden cardiac death and Chapter 8 of the NSF.

6.13 Equity of access

The service needs to ensure that it is accessible to all population groups and to find ways of both achieving and demonstrating this. In particular it needs to ensure that people from low income groups, the unemployed, those with low levels of education or with fewer personal resources are also able to find out about and use the services. Our survey did not find any evidence of services systematically addressing these issues although a number of services noted this as a problem (Box 6.19) and one service (Sheffield) noted this as an area for strategic development. The onus upon services to monitor the ethnic origins of their patients might also have important clinical consequences, given emerging epidemiological evidence suggesting that for some conditions, such as cardiomyopathy, there is an increased predisposition for the development of disease in certain ethnic groups (Dhandapany *et al.* 2009).

Box 6.19 Ensuring accessibility: findings from our survey

Three services noted accessibility as a gap in their service:

- *'groups that might not be accessing care include lower social classes, unemployed, people from ethnic minority groups and inner city groups. There are particular difficulties in caring for ethnic minority populations where there are communication problems or cultural issues including consanguinity. One challenge in addressing these problems is the need to develop a good database, but the service comments that this is a 'time-consuming process [that is being] stifled by the need to provide the clinical service'* (Sheffield)
- *'some geographic areas poorly represented in terms of referrals'* (Manchester)
- *'the service has been taken up by individual cardiologists for their patients on an ad hoc basis. Clinics have not been actively promoted, however cardiologists who have referred one patient frequently refer others or approach the cardiac genetic clinic for advice. This makes the service provision inequitable across the regions – a problem that can only be addressed if additional funding allows additional nursing and administrative staff to be appointed'*. (W Midlands).

Services need to be able to demonstrate equity of access by monitoring where their patients come from geographically and if possible their social origins such as from ethnic minority groups, lower social class or poorer levels of education. Our survey did not find any evidence of services systematically addressing these issues.

6.14 Service specifications and standards

All services should have a clear statement of the purpose of the service and the outcomes it is designed to achieve. Our survey findings (Box 6.20) show that formal descriptions of the service, its objectives, components and standards are not in place for most services.

Box 6.20 Objectives and quality standards for the ICC service: findings from our survey

Services were asked to provide documents such as service prospectuses, service specifications, aims and scope of the service and any commissioning documents. No service was able to provide us with a clear statement of purpose and a set of objectives. No service was able to supply a set of objectives.

Only the Sheffield service was able to provide a recent report that set out a current description of the service with background to the service need, principles on which the service was based, the overall remit of the services (conditions managed), specialists involved in multidisciplinary working, current service provision with some information on staffing levels and clinic provision, methods of working, provision of education to patients and other services and some evaluation of the numbers of patients seen in relation to the expected need in the population. This was the only service that referred to a quality agenda in which it included increasing access, rapid access for families with sudden cardiac death, improving services for disadvantaged groups, improving the transition from paediatric to adult services, the development of audit, research, patient support, education, and contributing to the development of services nationally through support to national charities and DH.

As discussed in Chapter 3, the available policy documents – in particular, Chapter 8 of the NSF for coronary heart disease, and the 'blueprint' document *Proposal for the Establishment of Inherited Cardiovascular Conditions Centres* (McKenna 2007) – do not adequately consider the necessary quality standards for the full range of ICC conditions. It is beyond the authority of the Working Group to set out appropriate quality standards for ICC services. However, as a result of this work the authors could produce an initial draft with a view to this being considered and further developed by an appropriately constituted national group.

Chapter 7 Ethical and legal issues

7.1 Introduction

The untimely death of a young adult as a result of an ICC is shocking not only because it may occur without warning in an apparently healthy young person, but also because it can bring with it knowledge that other family members may be at risk.

The NSF for Coronary Heart Disease recognised the distinctive needs of families in which an SCD has occurred, stating that NHS services should have in place methods to identify '*family members at risk and provide personally tailored, sensitive and expert support, diagnosis, treatment, information and advice to close relatives*'. In these families, the sharing of data and tissue samples is an integral part of the process of confirming diagnoses, establishing the genetic basis of disease and assessing the risk to relatives. However, as we have seen (Chapter 2), this process is often not clinically straightforward and requires knowledge of the legal constraints to the sharing of data and tissue, as well as the possible barriers to effective communication that can occur within families.

The aim of this chapter is to review the legal and ethical issues that arise when a suspected or definitive diagnosis of an ICC is made, either in a person who has died suddenly or in a living patient. As we have seen throughout this report, the interests of patients and family members in obtaining effective diagnosis and treatment usually coincide. Sometimes however there may be a tension between the rights and interests of the patient – the index case – and the clinical obligations that flow from that relationship, and the wider rights and interests of family members and obligations owed to them by health professionals. The most fraught ethical and legal issues arise where the interests of the index case and their relatives seem to be opposed. Examples include where a living patient vetoes the use of their tissue samples or personal data for the use of relatives who are identified by the health professional as being at risk. This chapter examines how some of those conflicts arise and notes current best practice. The chapter is adapted from a more detailed report prepared by the members of a subgroup formed for this element of the project. The members of the group are listed in Appendix 6.

7.2 Taking tissue samples from an affected person for the benefit of others: the Human Tissue Act

Cascade testing in the extended family must take account of the legal restrictions that apply to the sharing of tissue and data. The cornerstone of the legal framework for using human material such as tissue and DNA from one individual for the benefit of other family members is the Human Tissue Act 2004. The Act prescribes that explicit consent is required wherever the material is used for '*obtaining scientific or medical information about a living or deceased person which may be relevant to any other person (including a future person)*'. This means that explicit consent is needed if material from one family member is used to clarify another family member's susceptibility to genetic disease. Different legislative regimes apply to the retention, storage and use of human tissue and for the holding of DNA. It is now a criminal offence to use 'relevant' material (i.e human cellular tissue) for certain purposes (including use for the benefit of others) and to hold 'bodily' material and test the DNA within it for those purposes without consent. The Act does not apply to material held for medical diagnosis and/or treatment of the person 'whose body manufactured the DNA', or to material held within the coroner's jurisdiction. Nor does it apply to extracted DNA (since the remit of the Act is cellular material) although the implications of this distinction are not always clear.

Where material from a living person is required to be tested for the benefit of another family member, the Human Tissue Act provides that that person has an absolute veto over the use of their tissue, even if to deny others access to that tissue is likely to cause serious harm or death.

Where tissue or cellular material is needed from a relative who has died, the Act sets out a hierarchy of qualifying relatives whose consent is needed (unless the deceased person has nominated someone to act on his behalf in making such decisions). Problems may arise if the highest relative in the hierarchy refuses consent. For example a spouse, who is the highest qualifying relative, is not biologically related to the person who has died but has the power to refuse permission for tissue to be used for the benefit of biological relatives of the deceased person. For this reason, where material from a deceased person is held with the intention of analysing the DNA within it for the benefit of relatives, the hierarchy is unranked, which means that consent can be sought from any qualifying relative regardless of the proximity of their relationship to the deceased. In such circumstances the relative at risk of genetic disease will usually be asked to give qualifying consent.

7.2.1 Coroners

Some instances of ICC only come to light when an unexpected death is referred to a coroner for investigation. The scope of the coroner's authority is currently limited to investigating the case of death (UK Government 1984) and there is a complicated interface with the Human Tissue Act, which comes into effect once the coroner's authority lapses. Whilst the Human Tissue Act explicitly provides that material taken under the coroner's authority is exempted from the scope of the Act, difficulties can arise. Lack of clarity over the legal status of these samples means that where samples are taken in the knowledge that the information gained from them will be rolled out to at-risk family members, consent is required under the Human Tissue Act. In addition, codes of practice to the Human Tissue Act (Human Tissue Authority) and amended Coroners' Rules (UK Government 1984) dictate a default regime whereby tissue samples are destroyed if family members fail to consent to ongoing retention. The Coroner has no authority to authorise retention of human tissue once the cause of death has been certified. The lack of coherence in the legal framework affecting such samples has created a fragmented service which means that at-risk families are not receiving optimal care.

Best practice guidance where an ICC is suspected is for the whole heart to be retained and sent to a specialist service (Basso 2008). In practice, there seems to be considerable variability between regions in the nature and amount of post-mortem human tissue samples that are retained under the coroner's authority. Evidence suggests that concerns about the need to justify uses of post-mortem human material (particularly samples from babies and young children) account for some of this variation. Concern about the cultural sensitivities of some communities, and inadequate resources, may also play a part.

The Human Tissue Authority has responsibility for inspecting and licensing all facilities carrying out post-mortems (including coroners' post-mortems). A recent report of inspections by the Authority (Human Tissue Authority 2008) acknowledges that facilities are often poorly resourced and that many mortuary staff are unfamiliar with '*concepts such as governance, quality management and standards compliance*'. The report expresses the hope that a structured system of licences and inspections will raise standards over time.

Legislation to reform the coroners' system has recently been introduced into Parliament in the 2008–2009 Parliamentary session and a draft Coroners and Justice Bill was published in January 2009. Under current plans, the revised coronial system will be led by a Chief Coroner who will oversee a rationalised service which provides for a hierarchy of senior and deputy coroners within each area. The Bill provides for a unified system of death certification using independent medical examiners (medical practitioners having at least 5 years experience) employed by local PCTs, who will have responsibility for the independent scrutiny and confirmation of medical certificates. Regulations will amplify how to do so in a way that is 'robust, proportionate and consistent'. The requirement for medical examiners to have a knowledge of cardiac genetic conditions is likely to be an important component. Following the case of Shipman, there will also be an independent duty placed upon medical practitioners to notify deaths, and efforts made to support bereaved relatives during their contact with the coronial system (through publication of a charter for bereaved people).

Significantly, preliminary plans for reform include strengthening the powers of coroners to report to authorities which have the power to '*take action to prevent future deaths*'. Members of the subgroup together with various patient associations submitted a response to these draft proposals which advocates a purposive interpretation of this power, so that coroners will be obliged to take more proactive measures to reduce the risk of future deaths of family members. These include the requirement for medical examiners to have sufficient expertise to identify possible ICCs, for coroners to have authority to authorise retention of tissue samples for future use by relatives and where appropriate to disseminate copies of post mortem reports to the GP of the deceased person (who by that process can be alerted to the possibility of other relatives being at risk). The response also welcomed the commitment for relatives to be more engaged in the process of reform and standard-setting. An extended coroner's role implies that they will take a more active role in ensuring that at-risk family members are referred to local specialised medical services. The mechanisms for such referrals need to be worked out.

7.3 Establishing a diagnosis: issues for the patient and their family

As other chapters of this report have made clear, establishing a precise diagnosis of an ICC is a complex process requiring expert input from both specialist cardiologists and geneticists. In some situations, for example if the proband carries a mutation of uncertain significance, testing for the same variants in other family members may help to indicate whether the change is neutral or pathogenic. Box 7.1 illustrates some of the issues that may be raised by this situation, including the care and sensitivity needed in approaching other family members, and the difficulty of deciding when testing is or is not in their interests. Those proposing genetic testing should be mindful of the support that family members may need to reach an informed decision, especially if they have been recently bereaved.

As mentioned in Chapter 2, genetic investigation of suspected ICC may reveal gene–disease associations of uncertain significance. Care needs to be taken in communicating this information to patients since there is potential for clinicians to increase patient anxiety. This highlights the need for appropriate clinical expertise and if appropriate, access to therapeutic and bereavement counselling.

Box 7.1 Involvement of the family in establishing a diagnosis : Hypertrophic Cardiomyopathy

A 38 year old taxi driver is found at an insurance medical to have HCM with a thickened interventricular septum. There is no family history of HCM. He is asymptomatic. Clinical evaluation and investigation reveals no medical cause of hypertrophy. A synonymous base change is identified in exon 4 of the cardiac-myosin binding protein C gene. He is very keen that his two sons, who are 9 and 11 years old, are tested for this 'mutation'.

This request raises several key issues:

- is the molecular genetic finding pathogenic?
- if it is, at which age is the HCM in this family likely to develop and at what age should cardiological surveillance begin for 'at-risk' individuals in the family? In particular, when should children be tested?
- what are the implications for the siblings of this man? His elder sister age 43 years is a housewife and his elder brother age 41 years is an airline pilot.

Scenarios such as this require very careful and extensive clinical evaluation of the family, followed by a reassessment of the genetic results. Several members of the family may be drawn into the investigation. For example, if both of the taxi driver's parents are available for investigation, and comprehensive evaluation of both parents with clinical, echocardiographic and ECG assessment shows no features of HCM and genetic testing reveals that the mutation was *de novo* in the taxi driver (assuming paternity is certain), this would increase the probability that this is a disease-causing mutation. There would then be implications for the taxi driver's children but less likelihood that his siblings are at risk. The issues surrounding testing of children are discussed later in this chapter.

If the taxi driver's parents are no longer alive, investigation of his siblings might be suggested in order to help clarify whether the 'mutation' is pathogenic. However, the siblings may not welcome being approached for this purpose. The brother who is an airline pilot may fear that his job is in jeopardy if the investigation suggests he is at risk.

7.4 Sharing data

7.4.1 The legislative background

The clinical investigation of families in which an ICC is diagnosed or suspected involves the sharing of clinical and family history data as well as tissue samples. The legal basis for the sharing and processing of data from the living and the dead is established through a combination of the common law of confidentiality, the Data Protection Act 1998 (UK Government 1998a), the Access to Health Records Act 1990 (UK Government 1990) and the Human Rights Act 1998 (UK Government 1998b). In summary, the Data Protection Act (DPA) regulates the processing of identifiable data from the living. It sets out a series of data processing principles that dictate how those processing data should manage information, and provides for a more restrictive regulatory framework for those processing sensitive data (which includes medical data) than for those processing less sensitive information. The DPA also establishes a default position that consent should be obtained for processing medical data except where exemptions apply (such as where the processing is 'necessary for medical purposes' and is undertaken by a health professional or somebody owing an equivalent duty of confidentiality)'. Other specific exemptions apply for data processing that is judged to be in the public interest, such as disease notification to cancer registries and research involving anonymised data.

7.4.2 Where and what to record: family histories and genetic registers

Returns from the survey of services (Chapter 5 and 6) reveal variability in the professional groups delivering clinical services to those with ICCs. This has implications for the sharing of data across regions since the specialities of cardiology and clinical genetics differ in how medical notes are structured, held and shared. Many clinical genetics departments hold a pedigree sheet together with the notes of individuals from that kindred, in a set of linked case notes, and manage information on the extended family through links with other regional departments. Within cardiology, there is no tradition of holding records for the family unit, and notes for each individual member of a family are usually held in separate, unlinked case notes. More research is needed on the range of practices in current use in clinical genetics, cardiology and lipid clinics, and on how different systems can be rationalised to better serve the needs of families.

Disease-specific registries for cardiac conditions are useful resources but, due to lack of NHS funding, are few in number and usually held within the voluntary sector (for example, the Simon Broome register for FH). As contributions to registries are dependent on specific consent from patients, refusal by some patients can compromise the coverage and quality of the data. Whilst this could be addressed by introducing regulations to enable data to be transferred without consent (as for cancer registries) this might have the adverse effect of diminishing patient trust in health professionals. Any legislative change would need to be preceded by widespread public consultation and engagement.

7.4.3 Who, what, when and how to tell: obligations to the extended family

Within a clinical genetics setting, an individual diagnosed with an ICC is typically advised that any relatives who may also be at risk should seek referral to their local genetics clinic. However, in some contexts, research suggests that family members prefer to be approached by other health professionals. A recent study on cascade testing in FH has shown that here, the optimal strategy might be direct approach by a genetic nurse, provided that consent had been obtained from the index case (Newson 2005).

Cascade testing within the extended family must always be undertaken sensitively. There is a possibility that being informed of risk status may be perceived as an unwelcome invasion of privacy, or as a violation of the 'right not to know'. However, for the majority of the ICCs under consideration here, potentially life-saving interventions are available. Concerns about interference with privacy must be balanced against the benefits that appropriate diagnosis and treatment could confer.

Sometimes communication within a family breaks down, or rifts within families lead to refusal to share information. The consensus from international guidance is that disclosure of genetic information to identifiable at-risk relatives without consent is justifiable where the disclosure is likely to avert harm that is serious, foreseeable and highly likely to occur (by preventing or treating a disease or where early monitoring could impact upon reproductive choices) (Knoppers 1998). In contrast, as we have seen, a living person can veto the sharing of their human material on the same terms. The arguments for and against breaching confidentiality may be finely balanced and in practice geneticists very rarely inform relatives against their patient's wishes.

7.4.4 Sharing samples and information within the specialist service

Referrals for ICC services come from a variety of routes, and the services themselves are diverse. As a consequence, patient-identifiable information and samples often need to be shared between elements of the service including diagnostic laboratories, other specialist services (such as Grown Up Congenital Heart Services), FH services and complementary specialist cardiology and paediatric services. [As noted above, consent is not needed where tissue is used for diagnosis and treatment of the person whose body manufactured the DNA, and subsequent sharing of DNA extracted from that sample between diagnostic laboratories, even if shared for the benefit of family members, is widely

regarded as legitimate since the scope of the Human Tissue Act does not cover sub-cellular material such as DNA.]

Historically, it has not been routine practice to seek patient consent to the sharing of information between health professionals since sharing is justified on the basis of being in the patient's best interest. Within medical genetics it is now best practice to seek consent for family history information and, if appropriate, personal medical information to be shared with other relevant health professionals, and guidance has been developed. However, a more general code of practice on data sharing which could apply across specialities may be desirable and recent draft legislation making provision for wider data sharing between government departments seems likely to entrench the need for such a code.

The effective management of data from large kindreds that are geographically dispersed raises an additional set of problems. There is a lack of fully integrated software that can draw family pedigrees and manage data from a variety of different sources without breaching local data security protocols. The need to collate and integrate data from a number of different NHS Trusts, whilst ensuring that the provenance of data remains clear, and patient choices regarding sharing of their data are recorded and respected, exceeds the capabilities of existing IT systems. Given these shortcomings, it seems likely that policy initiatives that rely on nation-wide family-based follow-up systems being in place, such as the NICE guidance for FH, could be viewed as ambitious. Preliminary pilots of data management systems for cascade testing in FH are underway and results are encouraging, but such projects are limited in scope and capacity. Different service delivery models such as specialist cardiac genetics nurses employed by the BHF could be used to inform questions about data sharing between different providers.

However such initiatives fail to address inconsistencies in primary legislation, such as the requirement in the DPA for individuals to be notified by data processors when personal data are processed. Interpreting this requirement in the context of family history information is problematic and unresolved by guidance. With the development of novel sequencing technologies, it seems likely that managing the sheer volume of data, and providing for sufficient computational power to process those data, is in itself likely to prove challenging.

The impact of electronic patient records

The issues raised by genetic information are likely to become more pressing as a result of the planned introduction of nationwide electronic patient records across England and Wales. The NHS Connecting for Health IT scheme will introduce two types of electronic record: a summary care record initially comprising a diagnostic summary and prescription details, and a detailed care record that will hold a chronological medical history, and details of interactions with specific care givers. Whilst the summary care record will be held centrally and will be accessible by anyone able to prove legitimate access, detailed records will be provider specific.

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. For example, although summary care records can be created with only implied consent from patients, explicit consent to access records is required once they have been created. Arguably consents may need to be standardised and as generic as possible. More progress is needed to clarify the boundaries for legitimate data sharing between specialities and sectors.

7.5 Discrimination: insurance

Concerns that individuals are dissuaded from undergoing medically indicated genetic tests because of the fear of discrimination by insurers or employers have led to the UK insurance industry introducing a moratorium that prevents insurers from requiring predictive genetic tests to be carried out as a prerequisite to offering insurance (UK Government and Association of British Insurers 2005). This prevents 'high risk' test results from being used in calculating an increased premium or as a basis for

rejection (with the exception of high value policies for those at risk of Huntington's disease). Currently it seems that the Association of British Insurers is unlikely to modify its approach to predictive genetic tests once the moratorium expires in 2014. Insurers are permitted to use 'low risk' results to offset evidence from other sources such as family history and lead to insurance being offered at standard rates. Therefore in the short- to medium-term, concerns about adverse effects of genetic test results on an individual's ability to obtain insurance may be allayed, but questions remain about the long-term effect of the increasing use of predictive genetic testing on mutual (risk-rated) insurance.

There is evidence, in the case of FH, that insurers are prepared to reduce premiums for affected individuals who can demonstrate that they are lowering their risk by effective treatment. This may encourage patients who are deciding whether to undertake genetic tests for other treatable ICCs.

7.6 Testing of children

Many ICCs present in childhood or early adulthood and diagnostic genetic tests may be appropriate to confirm the diagnosis and guide management. The development of effective and affordable sequencing technologies seems likely to increase the use of tests over the next 3–5 years.

There is debate about whether children should undergo predictive or presymptomatic testing. This is because there is a tension between respecting the child's right to decide for themselves, and the parents' right to make decisions they believe to be in their child's best interests. For conditions with onset in childhood, or requiring surveillance in childhood, the decision to test is made after discussion between parents and clinical geneticists and is justified as being necessary in the child's best interests. Testing is usually deferred until just before the start of a surveillance regime. For some treatable adult-onset conditions (see Box 7.2 for the example of FH) there may be debate about where the balance lies between clinical benefit from early initiation of treatment, and respect for the child's autonomy.

As a general rule, children are not offered predictive tests for adult-onset conditions if there is no treatment or intervention available. If a treatment or intervention is available, best practice guidance (Clinical Genetics Society 1994) is that the decision to test is postponed until the child is competent to decide for themselves, unless screening or treatment is required to commence before the child becomes competent to consent. The legal basis for this process is established by the Gillick case, supported by the Children Act 1989 which allows a competent child to consent to treatment.

Box 7.2 Genetic testing of children for FH

The genetic testing of children and prompt treatment is clearly indicated for homozygous FH, because in the absence of treatment there is very early onset of cardiovascular disease. For the children of a parent with heterozygous FH there remains debate as to the appropriate age at which testing should be carried out (either by lipid measures or by a DNA test where a family mutation has been detected). In either case the justification for testing is that drug treatment (principally statins) should be started to offset clinical symptoms.

Vascular studies in children with FH have demonstrated that some children develop endothelial dysfunction by the age of 10. However for most individuals with FH, clinically evident vascular disease does not become evident until middle age. There is often a reluctance to prescribe lifelong medication in a child who is outwardly healthy, particularly if the lipid concentrations are not particularly high in adult terms, as well as concern that statins might interfere with growth and development. Because of this it has been common practice in the UK to defer statin therapy until after the age of 16 years in individuals with FH.

Current clinical evidence suggests a change to this approach. Controlled trials of statins in children and adolescents with FH have not shown any adverse effects on growth and development. Clinical experience would also indicate that diagnosis and initiation of medication is often more acceptable to a 10 year old than a rebellious teenager. In particular lifestyle advice has an important part to play in the management of FH, with both exercise and diet being important. Since smoking has a major potentiating action on the development of coronary atheroma in FH, it is particularly important that individuals with FH do not smoke. This is a key aspect for health care intervention in children and young people diagnosed with FH. Combined with increasing confidence on the overall safety and efficacy of statins, there is now a strong case for actively considering statin therapy in children with FH from the age of 10 onwards, especially in families with a history of early onset coronary disease.

7.7 Prenatal testing

Knowledge of the pathogenic mutation within a family allows the possibility of using that test before birth in prenatal diagnosis, with the option of termination of the pregnancy if the fetus is found to be affected. For the few disorders that manifest in early life and for which effective management options are not available (examples include Jervell Lange-Neilsen, Timothy or Andersen syndromes) this may be an option that some families may wish to explore in discussion with a clinical geneticist.

7.8 Conclusions

Legal constraints on the use of tissue and data belonging to one individual for the benefit of another individual have important implications for the management of families affected by the diagnosis of an ICC.

Current procedures following an unexpected death have several deficiencies that hamper the timely diagnosis of an ICC and the investigation of other family members who may be at risk. In particular, the coroner has insufficient powers to authorise ongoing retention of appropriate tissue samples for the benefit of surviving family members. There is a lack of coherence between the regulatory regime that applies during the coroner's jurisdiction, and the Human Tissue Act which applies once the cause of death has been established. These problems need to be addressed by legislative changes. There is also a need for coroners, medical examiners and pathologists to have appropriate education and training to ensure that they recognise the possibility that a death has been caused by an ICC, and

ensure that information is systematically forwarded to the appropriate services (ideally, both the deceased person's GP and the specialist ICC service).

There is uncertainty about the optimum methodology for cascade testing within extended families. Further research is needed to identify the most effective approaches so that practical guidance can be developed.

Within health services, there is inconsistency among different medical specialities in the way familial information is recorded, stored and communicated. Best practice guidance should be developed for consent and data sharing. There is a need to develop new IT systems that have the capacity to store individual diagnostic information together with familial information for extended kindreds.

7.9 Recommendations

The subgroup suggested several recommendations for regulatory, policy and clinical changes that impact upon ICC services. These are to be taken together with the recommendations made in chapter 9.

7.9.1 Recommendation A

Ensure appropriate retention of samples following a sudden cardiac death

- where an ICC is suspected as the cause of death, appropriate numbers and types of tissue samples should be retained on behalf of at-risk relatives in the future.
- consider recommending changes in legislation, including the following:
  - extension of the statutory role of the Coroner to ensure there is greater clarity on their obligation to 'prevent future deaths' and to retain samples from the deceased person so that appropriate enquiries can be made on behalf of relatives at a later date. This might require engagement with legislators and the relevant government departments as the Coroners and Justice Bill proceeds through Parliament.
  - amendment to the Human Tissue Act 2004 to support this role, for example to provide that the default position for samples retained under the Coroner's authority in cases of ICC is that they are retained for the future use of relatives rather than destroyed, and more generally to follow the precedent set in Scotland that blocks and slides from a deceased person are retained as part of that person's medical record.
- ensure that coroners, coroners' officers, medical examiners and pathologists are trained appropriately for their role and in particular that medical examiners should be trained in medical genetics (including cardiac genetics).

7.9.2 Recommendation B

Improve care for at-risk relatives following Sudden Cardiac Death

- ensure that coroners and coroners' officers have access to appropriate specialist medical expertise, to assist in the identification of at risk family members who may require ongoing advice and treatment and provide the relevant contact details.
- ensure that, if the coroner identifies a suspected ICC, information regarding risk to other family members is systematically forwarded to the deceased person's GP who may also have a duty of care to other family members.
- evaluate the methodology used in cascade testing and develop guidance.
- evaluate the role of cardiac disease registries not only as a demographic resource but as a means of improving patient care, such as increasing the effectiveness of cascade testing.

7.9.3 Recommendation C

Endorse relevant clinical guidance on consent and data sharing, and encourage more systematic consent processes

- ensure that written consent is sought from patients to share data and tissue for the benefit of other family members.
- promote the systematic practice of seeking consent from one family member for the benefit of others. This could include:
  - Developing a model consent form that is generally applicable across clinical specialities.
  - using a flow chart to illustrate the profile of data sharing, to include patient and family members; health care professionals from different specialties; schools; employers; insurers; coroners.
- promote best practice guidance for the storage, processing and retention of individual and family records or pedigrees.
  - promote the adoption of systems that have the capacity to store both individual diagnostic information and familial information, noting the provenance of data whilst safeguarding confidentiality and the autonomous choices of individual family members
  - more consideration is needed as to how to implement electronic patient records (such as Connecting for Health Healthspace) and how it could be best used to facilitate obtaining patient consent to the use of medical information, including genetic information.

Chapter 8 Horizon scanning: new technological developments and their potential impact on services

8.1 Background

Currently cardiac genetics services in the UK are focused on ICCs for which the underlying genes are known. Identifying the familial mutations in these genes can aid in diagnosis (including cascade screening), risk assessment, clinical management or reproductive risk counselling. Since mutational hot spots rarely occur, full gene mutation screening is invariably required to identify private familial mutations. This is quite laborious (hence expensive) using current technologies and limits the conditions for which genetic testing can be offered. Testing for moderately heterogeneous conditions such as hypertrophic and dilated cardiomyopathies and LQT syndrome, where up to 5 genes are currently tested, probably represents the diagnostic limits of current technologies. For some highly heterogeneous cardiovascular conditions, the genetic basis may be known but genetic testing may not be available because of the technical limitations of screening multiple genes.

Advances in genetic technologies and our increased understanding of the genetic basis of disease means that expansion of NHS genetic testing services to include testing for highly heterogeneous single gene disorders may now be possible. In addition, genetic variants affecting treatment response and susceptibility genes underlying complex diseases are being identified (Zhou 2008) and the prospect of pharmacogenetic testing in cardiovascular disease may also be realised in the near future. This chapter outlines some of these technological developments and the conditions for which genetic testing may become accessible as a result.

8.2 Next generation sequencing technologies

The major technological development on the horizon with relevance to cardiovascular disease is the development of next generation sequencing platforms. These technologies were originally employed for sequencing of the entire human genome and although they continue to be used primarily for *de novo* sequencing there is real potential for them to deliver targeted re-sequencing for clinical applications. These platforms (of which there are currently three, the GS-FLX offered by Roche, Illumina's GAII and the ABI SOLiD) are located in a few research centres in the UK, and programmes are already underway to evaluate whether the technology is sufficiently robust to be used in a routine NHS diagnostic setting. Although the next generation platforms have revolutionised the amount of sequencing data that can be produced, and the cost of doing so, there are still considerable challenges to routine use of the platforms. Firstly, the need for procedures that amplify the amount of DNA available means that the protocols are technically quite involved. Recently, however, array-capture methods have been described which involve hybridisation or annealing of the genes of interest to an array, and sequencing of these selected regions.

Whole exome arrays have now been launched and may obviate the need for targeted sequence capture. As their name suggests, these arrays allow sequencing of every exon (coding region) of every gene in the genome (hence exome) without prior knowledge of, or bias towards, specific candidate genes. Although this excludes the intronic regions and any splice sites or regulatory regions that may be contained within them, our current understanding suggests that the exonic regions are most likely to harbour the variants that compromise gene function.

Next generation sequencing platforms are limited by the volume of data generated and the bioinformatics and statistical genetics expertise required to manage and analyse the data. The data pipeline needs simplifying before the platforms can be used in the clinical arena. Programmes addressing these constraints are underway.

However, several 'next, next generation' sequencing methods are already in development from companies such as Helicos, Pacific Bio and Oxford Nanotechnology and are real contenders as clinical platforms. Some of these instruments (for example Helicos) have already been launched and it is likely that they will find clinical application within 2–3 years.

With regard to cardiovascular applications, next generation sequencing would allow faster and more comprehensive genetic testing for several cardiovascular conditions. Technological limitations confine genetic testing for SCD syndromes (hypertrophic and dilated cardiomyopathies, ARVC, and LQT syndrome) to the principal 4–5 genes, yet many other genes are known and cheaper sequencing costs would eliminate the cost-benefit concerns about testing these. Very large genes underlying SCD syndromes (*e.g. RYR2* as a cause of CPVT) could be tackled for the first time in a service laboratory setting. A genetic test for Marfan syndrome originally involved mutation detection in the fibrillin genes but the test was limited in its utility due to the apparent heterogeneity of the disease. Recently it has been shown that at least 10% of patients do not carry fibrillin gene mutations, and that mutations in transforming growth factor receptor genes TGFBR1 and 2, are important. Angiotensin II receptor blockers, such as Losartan, antagonise TGFB signalling and therefore represent important treatments for Marfan patients. This example demonstrates the importance of technologies that are sufficiently flexible to accommodate new genetic discoveries as they emerge. These new sequencing methods would also allow genetic testing for highly heterogeneous disorders such as congenital heart disease (for which hundreds of genes are known) to be embarked upon.

Recently, genome-wide association studies have led to advances in our understanding of the susceptibility factors underlying complex cardiovascular conditions such as coronary artery disease, hypertension and obesity which involve the interplay of genetics and environmental factors. Emerging candidate genes include the genes encoding cyclin inhibitors CDKN2A/B, MTAP (methylthioadenosine phosphorylase), ALOX5AP (arachidonate 5-lipoxygenase-activating protein) and LTA4H (leukotriene A4 hydrolase) for coronary artery disease, members of the dopamine signalling pathway for hypertension and the *FTO* (fat mass and obesity) associated gene for obesity. Although in general typing of a panel of known variants or single nucleotide polymorphisms (SNPs) may be sufficient to determine an individual's risk of these complex diseases, in time reductions in the cost of sequencing and the need for typing of multiple genetic variants may mean that sequencing replaces SNP typing as the method of choice. Next generation sequencing methods will certainly be important in the discovery and validation of novel susceptibility genes due to the potential to target whole pathways such as those involved in lipid metabolism and hypertension.

The era of personal genomics, where an individual's genome is sequenced to identify their private risk factors for different conditions, has already begun in the US but is considerably further away in the UK.

8.3 SNP typing

SNP typing methods will be important for the pursuit of pharmacogenetic applications relating to cardiovascular disease. Response to therapy or avoidance of side effects can be explained by genetic variants in drug metabolism genes (for example the genes encoding cytochrome P450s (Ingelman-Sundberg *et al*. 2007)) or in target genes. Warfarin, for example, is a commonly prescribed anti-coagulant for patients at risk of thrombosis, yet a significant proportion of patients on Warfarin (approximately 20%) experience major or minor bleeding events. Response to the drug is known to be influenced by variants in the *CYP2C9* and *VKORC1* genes. Knowing a patient's genotype may aid in initial warfarin dosing so that such side effects can be avoided (Gage 2008). Similarly, amongst patients with an acute myocardial infarction treated with the anti-platelet therapy clopidogrel, those with *CYP2C19* loss-of-function alleles had hyporesponsiveness and a higher rate of subsequent cardiovascular events. Statins are cholesterol-lowering drugs considered to be sufficiently safe that they are available over the counter in the UK. However, a minority of patients develop myopathy on high doses of the drugs. Recently, a genome-wide scan showed association of myopathy with common variants in the anion

transporter SLCO1B1, which has been shown to regulate the hepatic uptake of statins (Link 2008). This finding will enable those needing statins, but at risk of myopathy, to be identified prior to treatment. It is very likely that pharmacogenetic testing for these and other cardiovascular drugs will find clinical application in the not too distant future.

The success of recent whole genome association studies suggests that single nucleotide polymorphism (SNP) typing for susceptibility to complex cardiovascular conditions may be clinically useful in future. More research is needed to replicate existing SNPs and identify new ones which singly or in combination confer an odds ratio that justifies clinical typing. Nonetheless, predisposition testing of patients with coronary artery disease is on the horizon.

8.4 Array-based comparative genomic hybridisation (CGH)

In addition to a greater understanding of the role of SNPs underlying complex disease and response to drugs, there has been increasing awareness of the pathogenic role of larger genomic imbalances. Losses and gains of chromosomal regions can give rise to syndromic and non-syndromic cardiovascular conditions including congenital heart disease. For some of these conditions, such as DiGeorge syndrome, Williams-Beuren and Jacobsen syndromes, the regions of imbalance have been known for some time and fluorescent in situ hybridisation (FISH) tests developed to aid diagnosis. However, individual test costs are sufficiently high to prohibit testing of multiple loci unless there is a high degree of clinical suspicion about the syndrome or its underlying imbalance. Although karyotyping provides a genome-wide method for assessing chromosomal imbalances, the method is limited by the resolution of the light microscope (approx 5 Mb) and increasingly much smaller duplications and deletions are being identified with the advent of new microarray based methods. In particular, array-based comparative genomic hybridisation is proving to be the method of choice for detecting these and the improvements in probe density allow increasingly small imbalances to be detected.

Platforms for CGH have already been implemented in a number of NHS Regional Cytogenetics Labs where to date they have predominantly been commissioned for diagnosis of learning disability and dysmorphisms. Cost issues have prevented more widespread application but ongoing technological developments in probe density and multi-sample format arrays have already led to major cost reductions to the point where CGH arrays could be used as a first line test instead of karyotyping. These technologies are currently being investigated for cardiovascular conditions such as congenital heart disease where there is considerable unmet clinical need. Indeed, a targeted congenital heart disease CGH array has been produced and is currently being evaluated in a translational research programme.

Currently American Heart Association guidelines (Pierpont 2007) only recommend that genetic testing be carried out for children with congenital heart disease where there is a family history of the disease or for those for whom there is a high degree of clinical suspicion about the underlying pathogenesis. In practice, this means that many children and very few, if any, of the adult patient population is offered testing. Since many congenital heart disease patients are now reaching adulthood due to improvements in treatments and clinical management, reproductive risk counselling is an important additional benefit of such improved diagnostic methods. Both genome-wide and targeted arrays are being developed. The latter have the benefit of allowing discovery of previously unknown regions of imbalance. Targeted arrays, incorporating known cardiovascular genes, have the advantage that the precise genetic cause of congenital heart disease can sometimes be identified.

8.5 Expression profiling

Expression profiling in cardiovascular disease has been limited by the difficulties of biopsying heart and vascular tissue. The role of microRNAs in controlling cardiac gene expression is being elucidated through animal models and tissues from patients with end stage heart failure but clinical application is still some way off. Many expression profiling methods require fresh frozen tissue to ensure that the integrity of the RNA is not compromised. This requires pathologists to be present at operations and

limits the likelihood of expression profiling being adopted as a routine clinical procedure. If methods compatible with formalin-fixed, paraffin embedded tissue are developed this situation could change.

8.6 Conclusions and recommendations

For decades, genetic testing in the NHS has been confined to single gene disorders where 1–2 underlying genes are known. New technologies are dramatically changing this, by allowing the identification of novel genes and providing methods for more heterogeneous single gene disorders and even complex genetic conditions to be tackled in routine diagnostic labs. Some technologies have already been implemented, such as array CGH, but recommendations for inclusion of these in the NHS portfolio of tests need to be made on a case by case basis to practitioners and commissioners, based on the results of translational research. Such translational research is already being undertaken for congenital heart disease where a targeted CGH array has been designed and commissioning decisions will be required within the next 1–2 years.

For many pharmacogenetics applications the research data are robust and there are compelling clinical reasons for undertaking such evaluations. Translational research projects may be required to catalyse clinical uptake of this knowledge, but such testing needs to be considered for funding with some priority.

For other technologies, such as next generation sequencing, the impact is likely to be tremendous and pilot studies are already underway to assess how these technologies can be exploited for clinical use. NHS implementation of these platforms could occur in the next 2–5 years. We can expect to see a greatly expanded range of clinical genetic testing for cardiovascular disease that encompasses highly heterogeneous complex cardiovascular diseases. It is important that policy makers and commissioners recognise these dramatic changes and prepare for them if patients are to benefit from our increasing understanding of ICCs.

Chapter 9 Recommendations for ICC services

The speed of advancing basic science and development of clinical applications in inherited cardiovascular disease make it imperative that an infrastructure of clinical services is developed now. It is evident already that in some parts of the country, both in the capital and elsewhere, patients have benefited from the clinical services developed by those with major research programmes in ICCs, whereas others have lagged behind. Patients and their families are not well managed now in many parts of the country.

In cardiovascular disease as in most other clinical areas the complexities of care show every likelihood of increasing. We envisage in the near future, for example, that more genetic tests will become available, for a wider range of conditions, possibly even for complex cardiovascular conditions, and probably at a cheaper price. The complexity of knowing how to use and interpret these tests will not diminish. There will be more options for preventive management and treatment, requiring fine tuning to the underlying molecular abnormality. Without expert clinical organisations in all regions to provide a framework for development, the translation of science into good clinical practice will be slow and the checks and balances to prevent inappropriate, inexpert and inefficient care will be absent.

9.1 ESTABLISHING A STRATEGY

Recommendation 1

Each cardiac network should ensure that its population has access to specialised expert ICC services for children and adults. The scope of ICC services should include:

- **inherited arrhythmia syndromes (including SADS)**
- **cardiomyopathies, including cardiac manifestations of muscular dystrophies**
- **inherited arteriopathies (for example Marfan syndrome)**
- **disorders of cholesterol metabolism that cause coronary atherosclerosis.**

Although not within the scope of ICC services, given the interface with services for congenital heart disease (both paediatric and adult), lipid disorders and rare neuromuscular disorders that affect the heart, ICC centres should ensure they have close links with these services locally.

Recommendation 2

Most cardiac networks should not seek to develop their own ICC service. However they should ensure their population has access to a full range of services that meet agreed standards. Cardiac networks and those responsible for them at a national level should discuss and agree an indicative size, number and distribution of services. Because of the need to concentrate development and to ensure critical mass, the Working Group recommends that a relatively small number of services are supported in the UK (probably around 10 services outside London). In order to ensure that current expertise is not lost, where services are in close proximity, this might best be achieved by consolidation and integration of services.

The most effective means of affording universal access to specialised services is via cardiac networks. However, in view of the range of expertise required to deliver high quality services, it would be inappropriate for each cardiac network to seek to develop their own ICC service. Cardiac networks within each region should work together to identify where services should be consolidated to ensure that their populations have access to the full range of services.

Recommendation 3

Across the UK providers and commissioners of ICC services should anticipate and plan for a steady increase in demand within the next 5 to 10 years. In many areas this may require an expansion of several-fold to cope effectively and equitably with the needs of patients and families.

In Chapter 5 we provided evidence of inequity in provision of services between London and the regions and between some of the better provided and more poorly provided areas of the UK. In terms of patient activity there would need to be an approximately 3–4 fold increase in capacity to enable equal access to specialist services across the country.

The Working Group thought it likely that services would face this level of need over the next 5–10 years as a result of cascade testing, greater awareness and patient demand, more knowledge of the various clinical conditions, and better treatments. In theory this expansion would eventually be balanced against saturation of the prevalent pool of patients through effective identification of patients. However, current referral trends, and observations that cascade testing rarely identifies patients already known to the system, suggest that services are many years away from identifying all affected individuals. Further, the complexity of diagnosis, and in particular the need for relatively expensive and hard to interpret genetic testing, and the fact that many patients will need ongoing care, may also preclude the development of simple systems that would allow patients to be managed safely in a less specialised cardiology setting.

Nevertheless, in promoting the further development of services, the Working Group emphasised the need to ensure efficient systems in which diagnosis, management and care was devolved as much as possible through hub and spoke and shared care arrangements. It also noted that ICC services operate in a health service with many competing priorities and would need to demonstrate their effectiveness through good evidence on outcomes.

Recommendation 4

An Expert Advisory Group should be established, to guide and provide expert input for major strategic development. It should be multidisciplinary and include the perspectives of commissioners and voluntary organisations. In order to make significant progress the Group should include a small number of lead clinicians, public health professionals and administrative staff with dedicated time and should have resources to undertake a modest programme of stakeholder engagement, travel and other related activities.

9.2 COMMISSIONING

Recommendation 5

Formal and explicit commissioning mechanisms for ICC services should be developed by the cardiac networks in collaboration with commissioners of cardiac services and specialised commissioners for genetic elements of the services. These should reflect the need to provide high quality expert services balanced against reasonable geographic accessibility and should conform to the aspirations in World Class Commissioning.

Whilst recognising the equally important input of both cardiology and genetics to diagnosis and assessment for this group of patients and their families, the underlying clinical need for care is related to phenotype (pathology of the cardiovascular system) rather than the genotype (genetic abnormalities or variants). We recommend, therefore, that cardiology should be the lead clinical service with expert input provided by genetics. Cardiology services are commissioned through the cardiac networks and genetics services by specialised commissioners. Network commissioners must therefore work closely with cardiac commissioners and specialist commissioners for genetic services

to ensure that the necessary integrated service is provided for their population and that the services commissioned conform to the aspirations set out in World Class Commissioning (http://www.dh.gov.uk/en/managingyourorganisation/commissioning/worldclasscommissioning/index.htm).

Recommendation 6

Cardiac networks should commission an ICC Commissioning Framework via the Expert Advisory Group. This framework will give quantitative and qualitative guidance on the services that should be provided and their integration with primary, secondary and other specialised services.

A commissioning framework for ICCs will assist primary care trusts, commissioners at local and regional level and cardiac networks in organising and delivering efficient and high quality services. It also informs patients' and families' expectations of NHS services by providing indicators of high quality care. Such a guide should: set out the strategic context; propose key aims for ICC services; suggest important elements of needs assessment for local commissioners; and offer some indicators of high quality care (see standards recommendation 7) to assist local service review and inform service development.

Recommendation 7

Professional groups should take the lead in developing and agreeing a set of standards for specialised ICC services. This would include a description of the required skills and facilities, indications of expected activity, organisational aspects, audit and research. The specification should include a minimum immediate standard.

Chapter 6 sets out the Working Group's recommendations for a specialised ICC service that encompasses the professional competences of the various professionals involved, access to specialised tests and services, multidisciplinary teamwork and supportive organisational, educational and research elements. This description would form the basis for development and publication of a set of standards for services which should be agreed by providers and commissioners.

Recommendation 8

Cardiac networks should ensure that, by service developments, local consolidation and collaborative mechanisms, the ICC service for their patients sets out a realistic plan for reaching agreed standards within an appropriate time frame. Services that do not currently reach minimum standards should not be characterised as ICC services.

Whereas for most services published ICC standards would currently be aspirational, the Working Group recommends that services should produce a plan to achieve them in an appropriate period of time.

The Working Group also recommends that all services claiming to provide for the ICC patient group should be assessed against agreed minimum standards. Those services that do not reach such standards should not be characterised as ICC services for the purposes of centrally recommended or specialist-to-specialist patient referrals.

9.3 EDUCATION

Recommendation 9

Professionals from the range of ICC services should work with appropriate professional organisations, regulatory bodies, educational institutions and providers of specialist training to develop a workforce with the necessary specialist competences in the clinical, laboratory, pathology and allied professional groups. This should include continuing professional development and higher specialist training.

Expansion in ICC services requires growing a skilled workforce with the necessary sub-specialisation and also enhancing the competence of relevant professionals whose work is integrated with the specialist service – for example by recognising and referring patients or by being involved in shared care. It is expected that the major impetus for this will need to come from professionals within current ICC services.

It is important that a cadre of professionals with special expertise in cardiovascular genetics is produced in all relevant specialties through informal and formal training processes.

Lead professionals should be identified in cardiology (including paediatric cardiology), clinical genetics, genetic counselling, cardiac nursing, pathology, lipidology (including paediatric lipidology) and for the associated investigative professionals to work with regulatory bodies such as the Postgraduate Medical Education and Training Board (PMETB), the Royal Colleges and the providers of education and training to develop, where appropriate, specialist modules, training programmes and placements and educational resources. This educational provision should extend to coroners, coroners' officers and medical examiners, assuming that current plans for coronial reform are implemented.

For those already in post, such as specialist nurses working within ICC services, competence frameworks should be developed, building on those developed by Skills for Health in conjunction with the National Genetics Education Development Centre (NGEDC). This would provide a benchmark for those in post, and Trusts employing them, to ensure an appropriately skilled workforce.

Recommendation 10

Professionals from the ICC services should work with the National Genetics Education and Development Centre to develop educational resources to improve competences in inherited cardiovascular disease in professional groups involved in primary, secondary or other specialist elements of care for ICC patients.

ICC services must be 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 cardiology, primary care, paediatrics and any of the secondary and tertiary specialties that interface with inherited cardiac disease have a necessary basic level of understanding and competence. The NGEDC has programmes to develop education in genetics for such professional groups. ICC professionals should work with NGEDC to embed cardiovascular genetics into these programmes and, in particular, to develop specific resources for postgraduate medical training in cardiology.

9.4 ENHANCING AND MONITORING THE EFFECTIVENESS AND EFFICIENCY OF SERVICES

Recommendation 11

ICC services should collaborate on the development and evaluation of systems of cascade testing in conjunction with regional genetics services, including the development of IT systems that can link individuals within families.

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

Unlike genetics services, most mainstream services including ICC services have not formalised their methods for cascade testing, and areas 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 ICC services undertake their entire cascade testing through the regional genetics service, those that are embedded within cardiology services may undertake this work themselves, though not always in a systematic way. Further, the predicted increase in volume of such work arising from cardiac and other specialities would probably overwhelm genetic services. These issues must be addressed if opportunities for preventing mortality and morbidity due to ICCs are to be realised. Progress in ICC services would provide a useful prototype for other genetic conditions in other areas of clinical medicine where cascade testing may be appropriate.

The Working Group is aware of the NICE recommendations on implementation of cascade testing for FH and the planned cascade testing in Scotland and the pilot cascade testing project in Wales using an IT system from the Netherlands. The Group recommends that, rather than constructing a 'stand alone' system for FH, ICC services should develop a family cascade system that can be used for services as a whole. Such systems for identifying, contacting, and advising at-risk relatives 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. Consideration should be given to the development of a national database of ICC patients and family members, which could be used for clinical audit, clinical diagnosis and treatment, and research. Both systems will require considerations of consent (to keep and share both clinical and laboratory records), systematic appraisal of different methods of family record storage and methods of contacting family members (taking account of relevant legal and ethical considerations, such as the need to respect individual privacy and the right of an individual not to know a diagnosis).

Recommendation 12

Systems need to be developed to ensure the appropriate retention of samples following sudden cardiac death, the promotion of best practice regarding consent and data sharing within clinical practice, and effective approaches to cascade testing. The responsibility of coroners to family members who may be at risk of sudden cardiac death requires clarification and strengthening. Each of these measures may require legislative change.

Existing legal and regulatory frameworks place barriers in the way of effective data and tissue sharing for the benefit of families with ICCs, particularly in cases of sudden adult deaths, and clarification is needed regarding the ongoing responsibility of coroners to family members who may themselves be at risk. Tissue samples should be systematically retained where an ICC is suspected as the cause of death, since their retention may promote effective diagnosis of the condition in at-risk relatives. This might require changes in existing legislation: firstly to amend the scope of coroners' authority to make their obligation to 'prevent future deaths' more explicit (under the Coroners and Justice Bill)

and secondly to amend the Human Tissue Act 2004 to ensure that tissue samples are retained (rather than destroyed) in cases of suspected ICC.

Clarification is needed regarding the nature of the obligations placed upon coroners (together with medical examiners) to identify at-risk family members and the extent of their ongoing responsibilities (such as to share information about the cause of death with the deceased person's GP).

All health professionals should be encouraged to obtain explicit written consent from their patients to share their data and tissue for the benefit of other family members.

Recommendation 13

The Genetics Commissioning Advisory Group (GenCAG) through the UK Genetic Testing Network (UKGTN) should undertake a review of laboratory provision and finance to ensure effective, efficient and equitable genetic test provision in the light of current test availability and likely future developments in testing technology. It is anticipated that this might involve recommendations to consolidate laboratory provision of ICC genetic tests in a small number of laboratories around the UK.

A recent survey for the Human Genetics Commission (HGC) highlighted genetic testing for cardiac conditions as a specific pressure point for the genetic testing budget as a whole. This situation has resulted from the very rapid increase in the number of conditions for which tests have been developed, and the genetic heterogeneity of ICCs. The shortfall in resources is expected to become increasingly acute as more tests become available. The HGC report suggests that the genetically heterogeneous ICCs are a key model system that should help focus the development of an overall NHS strategy to assess next generation genetic technologies (discussed in Chapter 8). The capacity of these systems and the demand for testing for ICCs will contribute to planning the laboratory service configurations required to make best use of these technologies.

To provide economies of scale, rapid reporting times and expertise in interpretation of results, it may be desirable to focus activity and resources in two or three laboratories that would provide a comprehensive testing service, replacing the current rather fragmented situation in which laboratories may set up testing services for a subset of genes of their choice (subject to approval by UKGTN and GenCAG). In addition, concentrating expertise in a small number of laboratories would in the longer term facilitate the development of applications of DNA typing for common disease, allowing both test provision and interpretation to be provided in designated laboratories with appropriate evidence base and quality assurance. This will also ensure that, where testing reveals unexpected single gene disorders, patients and their families will receive appropriate advice.

Recommendation 14

ICC services should set up coordinated audit programmes to evaluate service provision, activity and outcomes against agreed standards. It is envisaged that patient activity will be captured through national database systems such the central cardiac audit database, heart failure database, pacing database and SADS database.

Audit is a vital aspect in the development and provision of high quality services. Our Report argues for the provision of specialist ICC services, the development of which, in many locations, will be from a fairly low starting point. A monitoring and audit programme should track the provision and activity of such services across the UK. Building on agreed standards (as set out above), an initial step will be the development of a system for benchmarking ICC services.

As cascade testing programmes are developed for different ICCs 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 risks resulting from diagnosis or treatment. This will be particularly important for individuals who are found to be mutation-positive but asymptomatic.

9.5 TRANSLATIONAL RESEARCH

Recommendation 15

ICC services should collaborate in setting up research programmes designed to investigate disease incidence, prevalence, genotype-phenotype correlation, natural history and the evaluation of clinical care. It is envisaged that these studies will be facilitated by the setting up of a national case register.

Rapid progress in our understanding of the molecular basis of inherited cardiovascular disease, increased capabilities to undertake genetic testing, and developments in preventive and treatment options for arrhythmias and other ICCs will require careful translational research to ensure that they are put to best use for patient benefit.

Current assumptions about the management of symptomatic patients cannot necessarily be applied to asymptomatic individuals discovered by cascade family testing, nor 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 ICC service and other systems.

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, and disease onset and progression in mutation-positive individuals who have no identifiable clinical risk factors
- effectiveness of interventions including those based on genotypic sub-classifications
- development and evaluation of methods for family cascade testing.

Such studies will be essential to support future arguments for prioritisation of ICC services.

Recommendation 16

Clinical and laboratory experts within the ICC services should maintain an overview of emerging technologies and novel tests and work with research institutes, NHS Trusts, public health, patient groups and other relevant organisations to ensure that translational research programmes are set up which critically evaluate the clinical utility of such technological developments, consider the implications for clinical practice and ensure timely implementation into service provision.

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Glossary of Acronyms

ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
BHF	British Heart Foundation
CGH	Comparative genomic hybridisation
CMR	Cardiac magnetic resonance imaging
CPA	Clinical pathology accreditation
CPEX	Cardiopulmonary exercise testing
DH	Department of Health
DPA	Data Protection Act
ECG	Electrocardiogram
FAF	Familial atrial fibrillation
FH	Familial hypercholesterolemia
GenCAG	Genetics Commissioning Advisory Group
GIS	Genetic Information Service
GUCH	Grown up congenital heart disease
HCM	Hypertrophic cardiomyopathy
HIP	Health Improvement Programme
HRUK	Heart Rythmn UK
ICC(s)	Inherited cardiovascular condition(s)
ICCS	Inherited cardiovascular condition services
ICD	Implantable cardioverter defibrillator
LDL	Low density lipoprotein
LQT (S)	Long QT (syndrome)
NGEDC	National Genetics Education and Development Centre
NICE	National Institute for Health and Clinical Excellence
NSF	National Service Framework
PCT	Primary care trust
SADS	Sudden adult / arrhythmic death syndrome
SAECG	Signal averaged electrocardiogram
SCD	Sudden cardiac death
SHA	Strategic Health Authority
SQTS	Short QT syndrome
SNP	Single nucleotide polymorphism
THH	The Heart Hospital
UKGTN	UK Genetic Testing Network
VT	Ventricular tachycardia
WFHP	Wales Familial Hypercholesterolaemia Project

Appendices

Appendix 1

Inherited Cardiac Genetics - Background Document

Brugada Syndrome

Epidemiology

In 1989, Martini et al. (1) described six patients with apparently idiopathic ventricular fibrillation, three of whom also had a distinctive ECG pattern characterised by an upsloping ST segment in the right precordial leads in association with right bundle branch block and T-wave inversion. After a detailed clinical investigation, subtle structural abnormalities of the right ventricle were observed and documented. In 1992 Pedro and Josep Brugada (2) described the same ECG changes in eight patients who experienced cardiac arrest due to ventricular fibrillation. They were the first to describe this new clinical entity using now characteristic terms such as `right bundle branch block', `ST segment elevation', and `sudden death syndrome'. Clinical symptoms all derive from ventricular arrhythmias and their complications, which include syncope and tachycardia. The most serious risk associated with these arrhythmias is ventricular fibrillation and sudden death.

The Brugada syndrome (OMIM#601144) is often a familial disease displaying an autosomal dominant mode of transmission with incomplete penetrance and an incidence ranging between 5 and 66 per 10,000 (3). Brugada syndrome is more prevalent in East and Southeast Asia, being described as Sudden Unexplained/Unexpected Death Syndrome (SUDS/SUNDS) (4; 5) with a male:female ratio of 8:1 (2; 6). Brugada syndrome and SUDS/SUNDS have been phenotypically, genetically and functionally determined to be the same disease (7; 8). The average age of patients experiencing arrhythmic events is 40 years old, and sudden death can occur at any age, including very young children (range 2 days to 85 years) (2; 6; 9; 10).

In 1998, Chen et al. (11) reported the first gene to be linked to Brugada syndrome. In their study, six small families and two sporadic cases were used to screen a variety of ion channel genes for mutations. In three of these families, mutations in the cardiac sodium channel gene SCN5A on chromosome 3, which encodes the α-subunit of the sodium ion channel, were identified. These mutations lead to a decrease in or loss of function resulting in altered protein trafficking and the eventual development of cardiac arrhythmias (12). However, of patients diagnosed with Brugada syndrome, only 18% to 30% have a mutation in the SCN5A gene (11; 13; 14). The SCN5A gene was excluded as the causal gene in a single family by Chen et al. (11) showing that genetic heterogeneity may exist in Brugada syndrome. A second locus distinct to SCN5A on chromosome 3 was identified in one large pedigree (15) adding further support to the genetic heterogeneity of Brugada syndrome. This has been associated with mutations in the glycerol-3-phosphate dehydrogenase-1-like (GPD1-L) gene that produces an SCN5A channel interacting protein. It has also been identified in around 1% of sudden infant death syndrome, causing reduced inward sodium currents by failure of SCN5A trafficking (16; 17). Mutations in CACNA1C and CACNB2, that encode the alpha1- and beta2b-subunits of the L-type calcium channel, have been identified in around 4% of consecutive Brugada syndrome probands who have an associated short QT interval (18). The molecular defect results in a loss of function of the inward calcium current. Most recently there has been a single report of Brugada syndrome being associated with a mutation in KCNE3, a beta-subunit that appears to associate with the product of KCND3 resulting in a gain of function in the transient outward potassium current (Ito) compared to wild-type (19).The genetic basis in the majority, however, remains unknown currently.

Diagnosis

On ECG, Brugada syndrome is characterised by Type 1 ST-segment elevation (coved type, J-wave amplitude 2 mm, negative T wave, gradually descending terminal ST segment). There must be no other factors which could explain the ECG results (e.g. structural heart disease, electrolyte or metabolite disorders). In some patients who carry Brugada syndrome the ECG can transiently normalise or the ECG features may be continually absent and therefore need to be unmasked via the administration of a sodium channel blocker such as flecainide or ajmaline (14).

The ECG alone, however, is insufficient to diagnose Brugada syndrome. According to the current consensus document (14) at least one of the following features should be present:

- Documented ventricular fibrillation
- Self-terminating polymorphic ventricular tachycardia
- A family history of sudden cardiac death
- Type 1 ECGs in family members
- Electrophysiological inducibility (Electrophysiological study induces ventricular tachycardia (VT) or fibrillation (VF) in almost all Brugada syndrome patients with a history of aborted sudden death or syncope)
- Syncope or nocturnal agonal respiration

Treatment/Management

The identification of carriers with a high risk of sudden death is vital as an implantable cardioverter defibrillator (ICD) offers the only recognised protection (2). The ICD works by defibrillating (shocking) the heart when it detects VF or VT to restore normal rhythm. Currently it is clear that individuals who have suffered a previous cardiac arrest or blackout are at sufficient risk of recurrence to justify an ICD (14; 20). Asymptomatic individuals with a normal resting ECG that requires a sodium channel blocking drug to induce the type 1 ECG are at low risk and need only follow lifestyle measures (14; 20). The investigation and management of asymptomatic individuals with a spontaneously abnormal ECG is much more difficult and fraught with controversy. Some researchers advocate the use of electrophysiological studies to risk stratify these patients while others advise against its use (14). Prospective international studies are currently addressing this issue.

Quinidine has been shown to prevent symptoms and resolve the atypical ECG features, warranting more research into its use as an alternative or adjunct to ICD (21; 22). Treatment of electrical storms (recurrent VT or VF) can be achieved with infusion of isoproterenol and/or the use of quinidine (9).

It is also important to test the relatives of individuals with Brugada syndrome to identify those at risk. Anyone suspected of having Brugada syndrome should take steps with lifestyle adjustment to avoid factors which can unmask the Brugada ECG, such as tricyclic antidepressants, ß-adrenergic antagonists and fever (14).

Wolff-Parkinson-White Syndrome

Epidemiology

Almost 80 years ago in 1930, Wolff, Parkinson, and White (23) reported the combination of bundle branch block, abnormally short PR interval, and paroxysms of tachycardia in a series of young healthy patients with normal hearts. Wolff-Parkinson-White (WPW) syndrome (OMIM#194200) is a form of ventricular pre-excitation which arises from an accessory conduction pathway linking the atria to the ventricles (24). Normally, the atria and ventricles of the heart are electrically insulated from each other, except for at the atrio-ventricular node. In WPW an additional conduction pathway is present which can conduct more rapidly than the normal pathway and also in both directions. This can lead to supraventricular tachycardia (SVT) which is responsible for the symptoms of WPW. Patients with WPW

syndrome are prone to developing a variety of symptoms which include light-headedness, dizziness, palpitations, angina. There is also a risk of atrial fibrillation occurring and triggering ventricular fibrillation which can result in sudden cardiac death (24).

The majority of WPW cases appear to be sporadic with no clear familial links involved (14). However, a significant minority of cases display strong genetic basis for the syndrome with an autosomal dominant inheritance pattern (25; 26). Incidence for WPW syndrome based on the ECG criteria alone ranges between 1.5 to 3.1 per 1000 persons (25; 27-30). Age at onset is variable as is the disease aetiology. MacRae et al. (31) were able to identify a genetic locus on chromosome 7q3 through linkage analysis of a large family with inherited WPW syndrome. The gamma-2 regulatory subunit of AMP-activated protein kinase *PRKAG2* gene is located within this genomic region on chromosome 7 and has been investigated as a candidate gene (25; 32). Gollob et al. (33) were able to identify a missense mutation in *PRKAG2* (R302Q) which was also present in another unrelated family with inherited WPW syndrome. Further mutations have been identified and described (34) although much work remains to undercover the genetic basis of this syndrome.

Diagnosis

The WPW ECG is characterised by:

- a PR interval of less than 0.12 seconds during sinus rhythm
- a slurring of the initial phase of the QRS complex (called a delta wave)
- QRS complex duration greater than 0.12 seconds
- secondary ST-segment–T-wave changes directed opposite to the major delta wave and QRS complex changes.

To diagnose WPW these ECG findings should be found in conjunction with a history of tachycardia. Electrophysiological studies can be used to locate the accessory pathways.

Treatment/Management

In symptomatic patients, the main treatment is radiofrequency catheter ablation (RFCA). RFCA works by heating the tissue of the accessory pathway to damage it and therefore terminate conduction.

Individuals with a relative who has WPW combined with cardiomyopathy should also be considered for cardiac assessment because this phenotype is associated with the PRKAG2 linked form of WPW and may therefore be familial.

Familial Atrial Fibrillation

Epidemiology

Familial atrial fibrillation (OMIM#607554) is a condition that disrupts the heart's normal rhythm. First reported as being 'familial' as long ago as 1943 (35), familial atrial fibrillation is an autosomal disorder inherited in a dominant pattern. The condition is characterised by uncoordinated electrical activity in the atria (the heart's upper chambers) which causes an abnormal heart rhythm that is generally extremely rapid and irregular and can lead to dizziness, chest pains, palpitations, shortness of breath and syncope. The uncontrolled rapid ventricular response rate may eventually lead to ventricular dysfunction and heart failure. The loss of effective atrial contraction can also allow blood to clot resulting in an increased risk of stroke. While some individuals may remain asymptomatic, the onset of symptoms can occur at any age, with an increase in incidence and prevalence with increasing age (36).

Although the familial occurrence of atrial fibrillation has been known for many decades, only recently

have advances been made that have improved the understanding of this condition (37). Brugada et al. (38) first identified a genetic locus for familial atrial fibrillation on chromosome 10q22-q24. Their findings also revealed that not all of the families investigated were affected by the chromosome 10q22-q24 locus, suggesting genetic heterogeneity. The 6q14-q16 chromosomal region has been implicated by Ellinor et al. (39) in a large family again showing a dominant inheritance pattern. No causal genetic variants have been identified in either of these two regions as yet although candidate genes are known. However, several mutations have been identified in potassium channel genes. A causal mutation in the potassium voltage-gated channel, KQT-like subfamily member 1 (*KCNQ1*) gene, located on chromosome 11p15.5, was identified in a Chinese family with dominant transmission (40). The S140G amino acid change increases the flow of potassium ions through the channel formed by the KCNQ1 protein in the cardiac muscle cells leading to a disruption of the heart's normal rhythm. Yang et al. (41) identified the R27C amino acid change in the potassium voltage-gated channel, Isk-related family member 2 (*KCNE2*) gene, located on chromosome 21q22.12, in all affected members of two Chinese Han families. This mutation also appears to increase the flow of potassium ions through channels regulated by the KCNE2 protein although it is not yet known whether this is in itself causal or just associated with familial atrial fibrillation. Xia et al. (42) also identified a V93I amino acid change in the potassium inwardly-rectifying channel, subfamily J member 2 (*KCNJ2*) gene, located on chromosome 17q23.1-q24.2, in a single Chinese family. This mutation again leads to an increase in the flow of potassium ions. The minK (*KCNE1)* gene S38G variant has also been studied and is associated with an increase in risk of atrial fibrillation for the G allele (43). The functional significance of this variant is however currently unknown. These mutations identified thus far only account for a very small proportion of the familial form of the disease suggesting much work still remains (44).

Diagnosis

An ECG can be used to determine the presence of atrial fibrillation. As the condition can temporarily normalise, a Holter monitor may be required. Eliminating alternative explanations for the atrial fibrillation and the presence of a family history is highly indicative of familial atrial fibrillation.

Treatment/Management

The main use of medication in familial atrial fibrillation is to slow the rapid heart rate (e.g. ß-blockers) and prevent thromboembolism formation (e.g. heparin). Where medication fails to improve symptoms, an ICD may be fitted to restore the normal heart rhythm.

Long QT Syndromes

Epidemiology

Long QT syndrome (OMIM #192500) is an inherited condition characterised by an abnormally prolonged QT interval and a predisposition to developing life-threatening ventricular tachyarrhythmias. These cardiac arrhythmias can lead to recurrent syncope, seizure or sudden death arising from ventricular fibrillation. Clinical manifestations often first appear in childhood with syncope precipitated by exercise or emotional upset in the pre-teen to teenage years. Birth incidence is unknown but has been estimated at between 1 per 5000 to 1 per 7000 (45). Several conditions are grouped under Long QT syndrome, including, Romano-Ward syndrome, Andersen-Tawil syndrome, Timothy syndrome and Jervell and Lange-Nielsen syndrome. Each of these syndromes has different disease characteristics. For example, Timothy syndrome is characterised by long QT syndrome and syndactyly (webbing of the fingers and toes). Jervell and Lange-Nielsen syndrome, on the other hand, is characterised by profound congenital deafness and long QT. There is also considerable variation in the age at onset of symptoms. 30-50% of those with mutations associated with long QT remain asymptomatic for life due to incomplete penetrance. Conversely, the average age at death due to Timothy syndrome is 2.5 years.

Romano (46; 47) and Ward (48) observed patients with syncope due to ventricular fibrillation with a prolonged QT interval without deafness, distinguishing the autosomal-dominant Romano-Ward syndrome from the previously described autosomal-recessive Jervell and Lange-Nielsen syndrome. Long QT syndrome is generally autosomal-dominant in inheritance and caused by mutations in cardiac ion channel genes and their sub-membrane interacting proteins (ChIPs). Modell and Lehmann (49) reviewed more than 470 different mutations that have resulted in changes to the passage of ions through their respective cardiac ion channel. Several potassium channel alpha subunit genes (*KCNQ1, KCNH2*, and *KCNJ2)* and their beta subunits (*KCNE1* and *KCNE2*) have been implicated. The sodium channel gene (*SCN5A*) and calcium channel gene (*CACNA1C*) are also involved. The most common mutations cause loss of function in potassium channel genes *KCNQ1* and *KCNH2* and gain-of-function in the sodium channel gene SCN5A. Respectively, these account for ~60%, 35% and 5% of families with identifiable mutations (45). However, about 30% of affected families do not have identifiable mutations in these genes or the other genes associated with long QT. The following Table (Table 1) lists the known genes that contribute to Long QT syndrome. The proportion of sudden deaths in the general population that are attributable to long QT syndrome is probably low (50).

Table 1: Known genes involved in LQTS adapted from Newton-Cheh and Shah (143)

Gene	Gene Name	Mutation effect	Reference
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily member 1, LQT1	Loss of function	OMIM(*607542) (203)
KCNH2	Potassium voltage-gated channel, subfamily H (eag-related) member 2, LQT2	Loss of function	OMIM(+152427) (66)
SCN5A	Sodium voltage-gated channel, type V α subunit, LQT3	Gain of function	OMIM(*600163) (204)
ANK2	Ankyrin 2, neuronal, LQT4 ChIP (multiple ion channels)	Loss of function	OMIM(*106410) (136)
KCNE1	Potassium voltage-gated channel, Isk-related family member 1, LQT5	Gain of function	OMIM(+176261) (179)
KCNE2	Potassium voltage-gated channel, Isk-related family member 2, LQT6	Gain of function	OMIM(+603796) (1)
KCNJ2	Inwardly rectifying potassium channel, LQT7	Gain of function	OMIM(*600681) (150)
CACNA1C	Calcium voltage-dependent channel, L type α 1C subunit, LQT8	Loss of function	OMIM(*114205) (178)
CAV3	Caveolin 3, LQT9 ChIP (SCN5A)	Loss of function	OMIM(+601253) (197)
SCN4B	Sodium voltage-gated channel, type IV β subunit, LQT10	Gain of function	OMIM(#611819) (129)
AKAP9	Yotiao, ChIP (KCNQ1)LQT11	Loss of function	(47)
SNTA1	Syntrophin, , ChIP (SCN5A) LQT12	Gain of function	(193)

Diagnosis

Long QT is traditionally diagnosed by the Schwartz score (63) which is based upon a combination of ECG features (QT prolongation and T wave abnormalities), personal history (blackouts) and family history (long QT and/or sudden death). The presence of a pathogenic mutation in one of the genes known to cause long QT can be diagnostic but is often only confirmatory of the phenotype. In the context of genotyped families, however, predictive testing is useful as variable penetrance means that a majority of carriers do not satisfy the Schwartz score criteria for 'definite' long QT syndrome (64; 65).

Treatment/Management

ß-blockers are the first line treatment in most individuals with long QT syndrome and are effective in preventing cardiac events in the majority of cases. For those individuals who have a history of cardiac arrest, an ICD is indicated (20). For those who have blackouts despite attempted treatment with ß-blockers or have other high risk features such as Timothy syndrome, Jervell and Lange-Nielsen syndrome, severe QT prolongation, female gender in adults or the LQT2 subtype, an ICD may also be considered (20). Occasionally younger patients with severe disease can be treated with an operation, left-sided cervical sympathectomy, which has been successful in reducing events and mortality (66). Education on the avoidance of factors which may precipitate cardiac arrhythmia are important e.g. intense physical exertion such as competitive sports, certain medications and hypokalaemia (20).

Short QT Syndrome

Epidemiology

Only recently described as a clinical entity, short QT syndrome (OMIM #609620) is characterised by exceptionally short QT syndrome which can cause episodes of syncope and cardiac arrhythmia often leading to sudden death (67). The age at onset of symptoms can be extremely young, with some reported instances of neonatal sudden cardiac death. To date, very few patients have been described. Despite this, three potassium ion channel genes have been implicated. Brugada et al. (68; 68) directly sequenced multiple ion channel genes in two families and identified a mutation (N588K) in the *KCNH2* gene, located on chromosome 7q35-q36, that was present in all affected family members but none of the unaffected members. Hong et al. (69) also noted that this syndrome was clinically heterogeneous, with syndromes varying from atrial to ventricular fibrillation and sudden death in the three families identified with this *KCNH2 N588K* mutation. A missense mutation in the *KCNQ1* gene was identified in a 70 year old man with short QT syndrome by Bellocq et al (70). The third gene implicated thus far in short QT syndrome, the *KCNJ2* potassium ion channel gene, was identified in a 5 year old girl and her father who both had short QT syndrome (71). With time we should become more aware of the clinical presentation of this disease.

Diagnosis

As with long QT syndrome, ECG is the main diagnostic tool in short QT. At a heart rate of 60beats/min, a QT interval of less than 330ms is indicative of possible short QT syndrome. This should be in the absence of any other possible explanation for the short QT interval e.g. hyperthermia or high serum potassium. Inducible ventricular fibrillation at electrophysiological study, as well as a family history of sudden death or atrial fibrillation can also help to establish a diagnosis.

Treatment/Management

Those individuals with a history of syncope or aborted sudden cardiac death would benefit from an ICD. Due to the relatively recent identification of short QT syndrome, and the small number of known cases, there is little clinical evidence on drug therapy. However recent studies have suggested a role for certain antiarrhythmics such as quinidine.

Progressive Familial Heart Block (PFHB)

Epidemiology

Brink and Torrington (72) reported two types of progressive familial heart block, type I and type II. Type I progressive familial heart block (OMIM#113900) is an autosomal dominantly inherited cardiac bundle branch disorder. It is characterised on ECG by evidence of bundle branch disease such as right bundle branch block, left anterior or posterior hemiblock, or complete heart block, with widening of QRS complexes. Progression is seen from a normal ECG to right bundle branch block to complete heart block. Clinical symptoms manifest when complete heart block supervenes, either with dyspnea, syncopal episodes or sudden death. In progressive familial heart block type II, the onset of complete heart block is associated with narrow complexes. Type II is also autosomal dominantly inherited and tends to develop along the lines of a sinus bradycardia with left posterior hemiblock and clinically presents as syncopal episodes, Stokes-Adams seizures (syncope and seizure due to inadequate blood flow to the brain), or sudden death with complete heart block supervenes (72).

Mutation in the sodium channel gene, SCN5A, on chromosome 3p21 has been found to cause type 1 progressive familial heart block (73). A second locus has also been identified on chromosome 19q13.2-q13.3 although no gene has yet been identified (74). Within this region, the potassium channel gene, *KCNA7*, was sequenced in affected family members but no pathogenic sequence change was found (75). Linkage analysis has been performed in families with type II progressive familial heart block with only one region on chromosome 1q32 showing interest (76). No mutations have been found thus far in the candidate genes known to reside within that region.

Diagnosis

As PFHB I and II have different ECG characteristics, this technique is key to diagnosis. Type I is typified by ECG evidence of bundle-branch disease or complete heart block (conduction failure between the atria and ventricles) with broad QRS complexes. Type II presents with complete heart block and narrow QRS complexes thought to result from atrioventricular nodal disease.

Management/Treatment

Patients should be monitored with regular ECGs and if necessary a pacemaker implanted to protect against the life-threatening consequences of heart block.

Hypertrophic Cardiomyopathy (HCM)

Epidemiology

Hypertrophic cardiomyopathy (OMIM#192600) is a disease of the myocardium that is typified by ventricular hypertrophy with preferential hypertrophy of the septum and anterior left ventricle wall (45). Teare (77) was the first to report the asymmetric hypertrophy of the heart in young adults from the autopsy findings of nine cases of sudden death in six families. Hypertrophic cardiomyopathy is a heterogeneous autosomal dominantly inherited disease which often develops during childhood and adolescence but generally is not progressive in adults. Individuals with the disease may remain asymptomatic, develop myocardial ischemia, arrhythmia (which can lead to sudden death) or develop heart failure (45). Adult prevalence is estimated at 1 in 500 (78). To date, nine genes have been implicated in the disorder, eight of which encode cardiac sarcomere proteins. Mutations in these eight genes are found in 60-70% of families with hypertrophic cardiomyopathy with another 10% occurring as a result of de novo mutations.

Table 2: Genes known to be involved in HCM

Gene	Gene Name and location	Mutation type	Reference/s
MYH7	Myosin heavy chain 7, CMH1, Chromosome 14q12	Several mutations, some of which are associated with benign course (L908V, G256E, V606M), others with a high risk of sudden death (R403Q, R453C, R719W). It has been estimated that 40 to 50 percent of cases are due to mutations in this gene.	OMIM(+160760) (85)
TNNT2	Troponin T2, CMH2, Chromosome 1q32	Several mutations. It has been estimated that 15 percent of cases are due to mutations in this gene.	OMIM(*191045)
TPM1	Alpha-Tropomyosin, CMH3, Chromosome 15q22.1	Several mutations with a high incidence of sudden death. Estimated that three percent of cases are due to mutations in this gene.	OMIM(*191010) (206)
MYBPC3	Myosin-binding protein C, CMH4, Chromosome 11p11.2	Several mutations almost all of which lead to a truncated protein product. Mutations in *MYBPC3* lead to milder phenotypes than those in *MYH7*.	OMIM(*600958) (45, 46)
TNNI3	Cardiac Troponin 1, CMH7, Chromosome 19q13.4.	Several mutations identified. The Asp190Gly mutation is associated with an adverse phenotype with a significant number of sudden cardiac deaths in the families with this mutation.	OMIM(+191044) (135)
MYL3	Myosin light chain 3, CMH8, Chromosome 3p	The Met149Val and Arg154His mutations have been associated with mid-left ventricular chamber type of hypertrophic cardiomyopathy. The E143K mutation was found as a homozygous mutation in a individual with two unaffected carrier family members.	OMIM(*160790) (144, 152)
TTN	Titin (Connectin), CMH9, Chromosome 2q31	Arg740Leu heterozygous mutation identified in a patient with no known mutation in any other gene associated with disorder. Mutation was found to increase the binding affinity of titin for alpha-actinin.	OMIM(+188840) (168)

MYL2	Myosin light chain 2, CMH10, Chromosome 12q23-q24.3	Five mutations identified which affect calcium ion binding andphosphorylation.	OMIM(*160781) (86, 151, 184)
MYLK2	Myosin light chain kinase 2, Chromosome 20q13.3	Two point mutations resulting Ala87Val and Ala95Glu changes believed to result in a functionally abnormal protein leading to the stimulation of cardiac hypertrophy.	OMIM(*606566) (68)
MYH6	Cardiac myosin heavy chain-alpha 6, Chromosome 14q12	Arg795Gln mutation identified causing possible interference with light chain interaction.	OMIM(+160710) (52)
MTTL1	Mitochondrial tRNA leucine 1	3303C-T, 3260A-G mutations identified. 3250T-C mutation and 3303C-T mutations possibly involved in sudden infant death families.	OMIM(*590050)

Diagnosis

Diagnosis of HCM is dependent on certain ECG and cardiac echo criteria. These include measurements of left ventricular wall thickness and motion of the mitral valve by cardiac echo as well as QRS voltage on ECG. As cardiac hypertrophy can be secondary to factors such as hypertension or valvular aortic stenosis, these possibilities must be eliminated before a diagnosis of familial HCM is made. Mutation analysis to establish the affected gene in the family can allow for screening of at risk family members. Moreover, this will provide information about the likely disease course as this varies with mutation.

Treatment/Management

All individuals with familial HCM should have regular cardiac assessment to monitor the disease. Those patients at high risk of sudden cardiac death can have an ICD fitted to help protect them against this risk.

A range of drugs exist to manage specific symptoms. For instance, beta blockers may be used to relieve palpitations and calcium antagonists can similarly reduce palpitations and chest pains. In those cases where medical therapy has failed, surgery may be an option. One such option is surgical myectomy which removes some of the thickened muscle from the septum thereby relieving obstruction.

Dilated Cardiomyopathy

Epidemiology

Dilated cardiomyopathy (OMIM#115200) is a disease of the myocardium characterised by cardiac dilation and impaired contraction of the left or both ventricles in the absence of coronary artery disease, congenital heart disease or abnormal loading conditions sufficient to cause ventricular impairment (45). Dilated cardiomyopathy can be caused by a diverse array of factors, from alcohol excess to metabolic disorders to late pregnancy. Incidence has been reported at 20 per 100,000 per year and the prevalence is estimated at 38 per 100,000 (90). Hereditary dilated cardiomyopathy, which accounts for at least 25% of all cases, is a heterogeneous disorder in which many genetic abnormalities have been identified (Table 3) along with several chromosomal locations implicated (including chromosomes 2q14-q22, 6q12-q16, 6q23, 7q22.3-q31.1, and 9q13). Mutations in these

genes only appear to account for approximately 20 percent of familial dilated cardiomyopathy. The majority of familial DCM follows an autosomal dominant pattern, but autosomal recessive inheritance and X-linked inheritance has also been implicated.

Table 3: Genes involved in dilated cardiomyopathy

Gene	Gene Name and location	Mutation type	Reference/s
LMNA	Lamin A/C, Chromosome 1q21.2	Several missense mutations identified, although deletions and insertions also identified.	OMIM(*150330)
LBD3	LIM domain-binding 3, CMD1C, Chromosome 10q21-q23	Several missense mutations identified.	OMIM(+605906) (199)
TNNT2	Troponin T2, CMD1D, Chromosome 1q32	Missense mutations including Arg141Trp and Lys210Del.	OMIM(*191045) (78)
SCN5A	Sodium channel voltage gated type V alpha subunit, CMD1E, Chromosome 3p21	Asp1275Asn mutation	OMIM(*600163) (128)
TTN	Titin (Connectin), CMD1G, Chromosome 2q31	Several missense mutations identified.	OMIM(+188840)
DES	Desmin, CMD1I, Chromosome 2q35	Ile451Met mutation identified.	OMIM(*125660) (117)
EYA4	Eyes absent 4 (Drosophila homolog), CMD1J, Chromosome 6q23	4846bp deletion resulting in premature stop codon.	OMIM(*603550) (169)
SGCD	Sarcoglycan delta, CMD1L, Chromosome 5q33	3bp deletion and Ser151Ala mutations identified.	OMIM(*601411) (192)
CSRP3	Cysteine and glycine rich protein 3, CMD1M, Chromosome 11p15.1	Trp4Arg mutation identified.	OMIM(*600824(
TCAP	Titin-cap (Telethonin), CMD1N, Chromosome 17q12	Arg87Gln mutation identified.	OMIM(*604488)
ABCC9	ATP-binding cassette subfamily C, member 9, CMD1O, Chromosome 12p12.1	3bp and 4bp deletion and Ala1513Thr mutation identified.	OMIM(*601439)
PLN	Phospholamban, CMD1P, Chromosome 6q22.1	3bp deletion, Arg9Cys, and Leu39Ter mutations identified.	OMIM(*172405)
ACTC	Actin alpha cardiac muscle, CMD1R, Chromosome 15q14	Arg312His and Glu361Gly mutations identified.	OMIM(+102540)
MYH7	Myosin heavy chain 7, CMD1S, Chromosome 14q12	Several missense mutations identified.	OMIM(+160760)
TMPO	Thymopoietin, CMD1T, Chromosome 12q22	Arg690Cys mutation identified.	OMIM(+188380)
PSEN1	Presenilin 1, CMD1U, Chromosome 14q24.3	Asp333Gly mutation identified.	OMIM(+104311)
PSEN2	Presenilin 2, CMD1V, Chromosome 1q31-q42	Ser130Leu mutation identified.	OMIM(+600759)
VCL	Vinculin (Metavinculin), CMD1W, Chromosome 10q22.1-q23	3bp deletion and Arg975Trp mutation identified.	OMIM(*193065)
MYBPC3	Myosin-binding protein C, Chromosome 11p11.2	Asn948Thr mutation identified.	OMIM(*600958)

Autosomal dominant DCM

Autosomal dominant inheritance accounts for approximately 23% of all cases of DCM (97). Two major forms of autosomal dominant DCM are recognised: isolated DCM and DCM associated with cardiac conduction system disease. In many cases, there may also be a skeletal myopathy. Genes implicated in isolated DCM include cytoskeletal (δ-sarcoglycan, ß-sarcoglycan and desmin) and sarcomere protein genes (including α-cardiac actin, troponin T, ß-myosin heavy chain, troponin C and α-tropomyosin). Several genes associated with isolated DCM and conduction disease have been mapped, but only one, lamin A/C which encodes a nuclear envelope intermediate filament protein, has been identified. Mutations in lamin A/C result in atrial arrhythmia and progressive atrioventricular conduction disease that frequently precede the development of LV dilatation and systolic dysfunction by several years. Some mutations in lamin A/C result in DCM and conduction disease alone, whereas others lead to juvenile-onset muscular dystrophies (including Emery-Dreiffus muscular dystrophy) or familial partial lipodystrophy with insulin resistant diabetes.

X-linked dilated cardiomyopathy

X-linked inheritance accounts for between 2 and 5% of familial cases of DCM. Most cases are caused by Duchenne, Becker and Emery-Dreifuss muscular dystrophies. Isolated X-linked DCM, also caused by mutations in the dystrophin gene, was first described in 1987 in young males with severe disease and rapid progression of congestive cardiac failure to death or transplantation. The condition is characterized by raised serum creatine kinase muscle isoforms, but does not result in the clinical features of muscular dystrophy seen in Duchenne or Becker muscular dystrophies. Female carriers of Duchenne and Becker muscular dystrophies, as well as female carriers of X-linked DCM, develop DCM later in life, usually in their 50s, that is milder in severity than that in their male counterparts.

Diagnosis

Key to the diagnosis of DCM is echocardiography. Using this technique, DCM may be established by an ejection fraction < 0.45 and/or a fractional shortening of < 25%, and a left ventricular end diastolic dimension of > 112% predicted value corrected for age and body surface area. For familial DCM to be diagnosed, all other possible explanations for the cardiac echo results must be excluded.

Treatment/Management

The main goals of treatment in familial DCM are symptomatic relief, prevention of disease progression and the management of serious complications such as progressive heart failure and thromboembolism (see National and International guidelines).

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Epidemiology

Catecholaminergic polymorphic ventricular tachycardia (OMIM#604772) is a severe arrhythmic disease characterised by salvoes of exercise-induced bidirectional and polymorphic tachycardias which lead to syncope (45). The tachycardia may either self-terminate or degenerate into ventricular fibrillation which can cause sudden death. The phenotype often presents itself in early childhood, with typical age at onset 7-9 years, but asymptomatic patients until their mid 30s have also been described. CPVT is a heterogeneous disorder which can follow an autosomal dominant or autosomal recessive pattern. Thus far mutations in two different genes have been identified as causal. These are the cardiac ryanodine receptor gene, *RYR2*, located on chromosome 1q41-43, and the calcium buffereing protein called calsequestrin, *CASQ2*, located on chromosome 1p13.3-p11. *RYR2* mutations account for approximately 50-55% of cases of CPVT and are inherited in an autosomal dominant manner (98-102).

CASQ2 mutations are rarer and are inherited in an autosomal recessive pattern (103; 104).

Diagnosis

Structurally, the heart of an individual with CPVT is sound, thus diagnosis relies on ECG findings. A resting ECG in an individual with CPVT may be entirely normal; however exercise stress testing can elicit ventricular arrhythmias which allow a diagnosis of CPVT to be made.

Treatment/Management

Long-term treatment with high-dose ß-blockers can be used to prevent episodes of syncope in the majority of individuals. For those individuals with a history of recurrent cardiac arrest, the only method to offer protection against sudden cardiac death is the use of an ICD.

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

Epidemiology

ARVD/C (OMIM#107970) is a heterogeneous autosomal dominant heart muscle disorder that causes arrhythmia, heart failure, and sudden death (45). It is characterised by progressive replacement of the right ventricular myocardium with adipose and fibrous tissue. The prevalence is not well defined but is estimated to be between 1 in 1,000 to 1 in 10,000 (78). The mode of transmission is usually autosomal dominant with variable penetrance, but autosomal recessive forms are well recognised. Numerous genetic loci have been identified, most of which occur in genes that encode desomosomal proteins. An autosomal recessive syndrome characterised by ARVC, woolly hair and palmoplantar keratoderma, common on the Greek island of Naxos, is caused by a homozygous mutation in the gene encoding plakoglobin. Families with a similar cardiocutaneous phenotype caused by an autosomal recessively inherited mutation in the gene encoding desmoplakin are reported from other Mediterranean areas, India and South America. Desmoplakin also accounts for 16% of dominant ARVC cases. Other genes implicated only in autosomal dominant disease include plakophilin 2 (PKP2) desmoglein (DSG2) and desmocollin (DSC2).

Two non-desmosomal genes have also been associated with ARVC. Mutations in the ryanodine receptor gene (RYR2) were reported in association with a localised form of ARVC, but mutations in this gene more typically cause catecholaminergic polymorphic VT (CPVT) and are no longer classified as a sub-type of ARVC. A mutation in the transforming growth factor beta 3 (TGFß3) gene has also been described, but the mutation occurs in an intronic region of the gene, and only one of the three originally described ARVC1 families has a TGFß3 mutation.

Diagnosis

A range of cardiovascular assessment techniques are involved in identifying ARVD/C including: ECG, cardiac echo, cardiac MRI, electrophysiological study, right ventricular endomyocardial biopsy and right ventricular angiography. Diagnosis is made on the basis of a combination of major and minor criteria such as fibrofatty replacement of the myocardium and severe right ventricular dilation and reduction of function, with no (or only mild) left ventricular impairment.

Treatment/Management

Common primary aims of ARVD/C treatment are the prevention of syncope, cardiac arrest and sudden death. Main treatment options include the use of ß-blockers and implantation of an ICD.

Barth Syndrome

Epidemiology

First described in 1983 (105), Barth Syndrome (OMIM#302060) is an X-lined recessive disorder of lipid metabolism that affects males characterised by cardiomyopathy, neutropenia, skeletal myopathy, growth deficiency, and 3-methylglutaconic aciduria. The syndrome is rare with accurate incidence rates unknown, however, rates have been estimated in the USA at approximately 1 in every 300,000 to 400,000 births (106). More than a hundred mutations in the tafazzin (TAZ) gene, located on chromosome xq28, have been indentified in patients with Barth syndrome (107). Many of these mutations involve the introduction of a stop codon into the open reading frame which result in aborted protein translation (108).

Diagnosis

Clinical diagnostic criteria include growth delays observed in early infancy with a general decline in growth velocity over the first two years, the presence of cardiomyopathy within the first months of life initially presenting as hypertrophic or dilated cardiomyopathy, and often an increase in levels of 3-methylglutaconic acid. Finding a Barth TAZ gene mutation that disables the synthesis of the protein or its function can also be tested for, with prenatal testing possible in cases where mutation is known in the family.

Treatment/Management

Although there is no specific treatment for Barth syndrome, each of the individual problems may be successfully controlled with both the heart disease and short stature often resolving entirely after puberty (106).

Noonan Syndrome

Epidemiology

Noonan syndrome (OMIM#163950) is an autosomal dominant condition characterised by hypertelorism, a downward eyeslant, and low-set posteriorly rotated ears (109) with other features including short stature, a short webbed neck, congenital heart defects, deafness and motor delay. Incidence has been estimated at between 1 in 1000 and 1 in 2500 live births (110). Congenital heart defect occurs in 50 to 80 percent of individuals with pulmonary valve stenosis (often with dysplasia) the single most common heart defect, found in 20 to 50 percent of individuals (111). Hypertrophic cardiomyopathy is found in 20 to 30 percent of individuals and may be present at birth or appear in infancy or early childhood. Four genes are known to be associated with Noonan syndrome. Gain of function mutations in the protein-tyrosine phosphatise nonreceptor-type 11 gene, *PTPN11*, located on chromosome 12q24.1 have been identified in about 50 percent of individuals with Noonan syndrome (110; 112; 113). De novo mutations in the Kirsten rat sarcoma viral oncogene homolog gene, *KRAS*, located on chromosome 12p12.1, account for less than five percent of individuals with Noonan syndrome (114). Missense mutations in the son of sevenless Drosophila-homolog 1 gene, *SOS1* (guanine nucleotide exchange factor), located on chromosome 2p22-p21, have been identified in approximately 13 percent of individuals with Noonan syndrome, and in patients without mutations in the *PTPN11* or *KRAS* genes, *SOS1* mutations occur in about 20 percent of individuals (115; 116). The fourth gene known to be involved in Noonan syndrome is murine leukemia viral oncogene homolog 1, *RAF1*, located on chromosome 3p25, with mutations observed in 3 to 17 percent of individuals with Noonan syndrome (117; 118).

Diagnosis

The diagnosis of Noonan syndrome is made on clinical grounds by the observation of key features which are well delineated despite a lack of defined diagnostic criteria (119). Characteristic features include short stature, congenital heart defects, a broad or webbed neck, unusual chest shape with superior pectus carinatum, inferior pectus excavatum, apparently low-set nipples, developmental delay of variable degree, cryptorchidism in males, with facial characteristics such as low-set posteriorly rotated ears with fleshy helices, vivid blue or blue-green irides, eyes that are often wide-spaced with epicanthal folds and thick or droopy eyelids. Cardiovascular assessment is made using ECG and cardiac echo. In addition genetic testing is available to highlight mutations in the *PTPN11, KRAS, SOS1,* and *RAF1* genes.

Treatment/Management

The cardiovascular anomalies observed in Noonan syndrome patients are treated in the same manner as in the general population (111).

Loeys-Dietz syndrome

Epidemiology

Loeys-Dietz syndrome (OMIM#609192) is a heterogeneous autosomal dominant condition characterised by arterial tortuosity and aneurysms, hypertelorism (widely spaced eyes) and a bifid uvula or cleft palate (120). The major risk associated with Loeys-Dietz syndrome is aortic dissection or rupture at an early age (mean age at death 26 years). Loeys-Dietz syndrome is caused by mutations in the *TGFBR1* and *TGFBR2* genes, which encode growth factor receptors (121).

Diagnosis

Diagnosis of Loeys-Dietz syndrome can be achieved via CT or MRI angiography to detect aneurysms and arterial tortuosity. If this is established in combination with hypertelorism, a bifid uvula or cleft palate, then a diagnosis of Loeys-Dietz should be strongly considered. In addition, genetic testing is available to highlight mutations in the *TGFBR1* and *TGFBR2* genes.

Treatment/Management

The main aim is to manage the vascular consequences of the syndrome. This can be achieved through ß-blockers, exercise restrictions, frequent cardiovascular imaging and prophylactic surgical repair when the aortic root exceeds 5cm in diameter.

Thoracic Aneurysms and Aortic Dissections (TAAD)

Epidemiology

Familial thoracic aortic aneurysms and aortic dissections (OMIM%607086) is a heterogeneous autosomal dominantly inherited disorder. Normally as a result of degenerative changes in the aortic wall, the cardiovascular manifestations are characterised by the dilation of the aorta at the level of either the ascending aorta or the sinuses of Valsalva. Aneurysms and dissections of the thoracic aorta involve either the ascending or descending aorta (111). The age at onset and rate of progression of these potentially life-threatening symptoms is highly variable.

Several loci have been identified and mapped to date on chromosomes 11q, 5q, 3p and 16p. On chromosome 3p25-p24, mutations in the *TGFBR2* gene have been identified in 4 unrelated affected

families by Pannu et al. (122). These mutations were only estimated to account for approximately 5% of the inherited predisposition. Mutations in the myosin heavy chain 11 gene, *MYH11*, located on chromosome 16p13.13-p13.12, were identified by Zhu et al. (123) after systematic screening. Guo et al. (124) more recently identified missense mutations in the *ACTA2* gene responsible for approximately 14% of inherited thoracic aortic aneurysms and aortic dissections.

Diagnosis

Diagnosis of familial TAAD involves detection of dilation and/or dissection of the thoracic aorta (using CT, MRI or cardiac echo), the absence of Marfan syndrome and other connective tissue disorders, and the presence of a positive family history.

Treatment/Management

If properly managed, life expectancy for an individual affected by TAAD should approach that of the general population. This management includes aggressive control of hypertension, prophylactic surgical repair of the aorta as required, and continued surveillance. This surveillance should include imaging of the entire aorta every few years to detect aneurysms along its length. Individuals at risk of inheriting TAAD should also receive regular examination to allow early detection and intervention.

Ehlers-Danlos Syndrome Type IV (EDS IV)

Epidemiology

Ehlers-Danlos syndrome type IV (OMIM#130050) is an autosomal dominant disorder characterised by thin translucent skin, unsightly bruising and scarring, stereotypical facial appearance, musculoskeletal discomfort, susceptibility to osteoarthritis and arterial, intestinal and/or uterine fragility (45; 111). Joint mobility of the hand may also be increased. Arterial rupture is the main cardiovascular complication and the main cause of mortality (median life expectancy: 48 years). Neonates tend to present with clubfoot and/or congenital dislocation of the hips. In childhood, inguinal hernia, pneumothorax and recurrent joint dislocation are common. Presenting signs in the majority of adults tend to be vascular rupture or dissection, gastrointestinal perforation or organ rupture. Superti-Furga et al. (125) first identified a deletion mutation in type III collagen gene, *COL3A1*, located on chromosome 2q31 as causal in type IV Ehlers-Danlos syndrome. Further mutations have been identified in this gene (126-131).

Diagnosis

There are several major diagnostic criteria for EDS IV, including arterial rupture, uterine rupture during pregnancy and a family history of EDS IV. Minor criteria include thin, translucent skin and a characteristic facial appearance. These clinical observations can be supported by biochemical testing of type III procollagen production, its intracellular retention, secretion, and/or mobility.

Treatment/Management

The main management strategy in EDS IV is to avoid factors that may lead to damage to arteries or organs, such as contact sports. The other key task is to tackle such damage when it arises e.g. repair of bowel or arterial tears. This can be difficult due to the extremely fragile nature of the tissues.

Myotonic Dystrophy

Epidemiology

Myotonic dystrophy (OMIM#160900) is an autosomal dominant disorder characterised mainly by myotonia (involuntary muscle contraction with delayed relaxation) and muscular dystrophy, but can include cardiovascular manifestations (111). These manifestations tend to be cardiac conduction defects which cause arrhythmia leading to syncope and palpitations. Cardiologic abnormalities including bradycardia, prolongation of the PR interval-progression to complete heart block, left axis deviation (LAD) due to left anterior hemiblock (LAH), bundle branch block (LBBB or RBBB), bifasicular block (RBBB & LAH), and atrial fibrillation/flutter are observed. Cardiac arrhythmias are a significant cause of early mortality in type I (DM1). Cardiac involvement in type II (DM2/PROMM – OMIM#602668) is milder, although it can be associated with conduction defects, arrhythmias, cardiomyopathy and sudden death.

Type I (DM1) is caused by the expansion of a CTG trinucleotide repeat at the 3' end of *DMPK*, the gene that encodes the enzyme myotonin-protein kinase, located on chromosome 19q13.2-q13.3 (132). A CTG repeat length of between 4 and 37 is considered normal (45). Length variation in the CTG repeat number and severity of disease phenotype has also been observed. Mild late-onset disease is observed in individuals with 50-80 CTG repeats. The classic disease phenotype is observed with a CTG repeat size of approximately 100 to 1000 with congenital myotonic dystrophy observed in individuals with >1000 repeats (45; 111). Type II (DM2/PROMM) is caused by expansion in the CCTG repeat at the promoter end adjoining intron 1 in *CNBP (ZNF9*), the gene for cellular nucleic acid-binding protein, located on chromosome 3q13.3-q24. Thornton et al. (133; 134) reported patients with clinical characteristics consistent with classic myotonic dystrophy but without the CTG repeat in the *DMPK* gene. The disease locus was refined to chromosome 3q in a large five-generation family (135) before the CCTG expansion repeat in CNBP (*ZNF9*) was identified (136).

Diagnosis

A range of clinical tests can be used to diagnose myotonic dystrophy, including muscle biopsy and evaluation of muscle strength. Detection of the cardiovascular manifestations requires an ECG to pick up arrhythmias or a cardiac echo to highlight cardiomyopathy.

Treatment/Management

If cardiac involvement is established, patients should receive regular cardiac examinations via routine ECG and cardiac echo. Treatment with a pacemaker is advised when a progressive arrhythmia is detected, even if the patient is asymptomatic.

Criteria for EPS – invasive electrophysiological studies – in DM1, Lazarus et al (137)

1. 1st degree HB (PR>0.2) – with or without widening of QRS (>100ms)
2. palpitations with evidence of dysrhythmia
3. syncope/near syncope
4. in preparation for major surgery.

Symptomatic

- if severe ventricular dysrrhythmias consider ICD (implantable cardioverter/defibrillator)
- pace if HV >70ms

Asymptomatic – all patients with CTG repeats

- annual ECG
- Holter 2 yearly
- ECHO every 5 years
- EPS if 1) PR >0.20s; 2) QRS >0.12; 3) sinus dysfunction or AV block of any kind

DM11

- Full cardiologic evaluation as above, if normal no surveillance is recommended but if symptomatic then follow above treatment/management

Marfan Syndrome

Epidemiology

Marfan syndrome (OMIM#154700) is an autosomal dominant multisystem disorder of fibrous connective tissue which particularly affects the cardiovascular, skeletal and ocular systems. It affects 1 in 5000 population worldwide. In 75% of cases there is a positive family history. The cardiovascular complications in Marfan syndrome are the most common cause of morbidity and mortality among affected individuals. They include dilation of the aorta at the level of the sinuses of Valsalva, a predisposition for aortic tear and rupture and mitral valve prolapse with or without regurgitation, triscuspid valve prolapse, and enlargement of the proximal pulmonary artery (45; 111). Marfan syndrome is mainly caused by mutations in the fibrillin gene, *FBN1*, located on chromosome 15q21 (138-141). Fibrillin mutations can cause a broad range of phenotypes, from individuals at the extreme end of the normal spectrum to those who present as neonates with severe, progressive Marfan syndrome in multiple organ systems (142). An additional gene has also been implicated in Marfan syndrome type II. Type II was initially described in a large French family in which multiple members exhibited some of the skeletal and cardiovascular features of Marfan syndrome but lacked ocular abnormalities (143). Mizuguchi et al (144) identified a chromosomal breakpoint on chromosome 3q24.1 that disrupted the gene encoding TGF-beta receptor-2, *TGFBR2*, and further identified other missense mutations in unrelated probands.

Diagnosis

Diagnosis of Marfan syndrome is based on the Ghent diagnostic criteria (145), which focus primarily on the presence of major and minor criteria in the 3 main affected systems. Major involvement in 2 out of 3 systems (ocular, cardiovascular, and musculoskeletal) are required for diagnosis, for example ectopia lentis and aortic root aneurysm. Due to the range of systems involved, a variety of diagnostic tools are required. In the case of the cardiovascular system the use of MRI or cardiac echo is recommended to establish the aortic root size and shape, while skeletal measurements (height, arm span, upper segment/lower segment ratio) together with high palate, scoliosis, pectus deformity, and arachnodactyly provide evidence of marfanoid build.

In most centres it is also possible to perform a mutation analysis to detect *FBN1* mutations. The yield is 91% in cases of classical Marfan syndrome. Once a mutation is identified, it can be used for DNA screening of close family members, including prenatal diagnosis, and even preimplantation genetic diagnosis to ensure the birth of unaffected child. A causative mutation can make the diagnosis in cases which do not fulfil the Ghent criteria clinically. This is valuable when the patient is a child who has not yet developed the full syndrome (146).

Treatment/Management

Management of Marfan syndrome requires a multidisciplinary team of specialists to tackle the manifestations in each of the different organ systems. To manage the cardiovascular complications, patients should have annual echocardiography to monitor aortic root dilation (more frequently in those with a dilation of > 4.5cm). ß-blockers may also be of use to slow dilatation once the aortic diameter exceeds the upper normal limit. Patients whose aortic root diameter measures 5cm or more in the sinuses of Valsalva should be referred for replacement of the aortic root, with or without aortic valve preservation.

Emery-Dreifuss muscular dystrophy (EDMD)

Epidemiology

Emery-Dreifuss muscular dystrophy is a heterogeneous disorder that can follow X-linked (OMIM#310300), autosomal dominant (OMIM#181350) or autosomal recessive (OMIM#604929) inheritance patterns. It is characterised by slowly progressive muscle wasting and weakness, early muscle contractures (tightening around elbow, hands, and knees which limits movement) and cardiac disease with conduction defects and arrhythmias (111). The age of onset, severity, and progression of muscle and cardiac involvement is highly variable. Key cardiac features can include palpitations, syncope, congestive heart failure, ventricular arrhythmias, dilated cardiomyopathy and sudden death despite pacemaker implantation (147). The risk of ventricular tachyarrhythmia and dilated cardiomyopathy manifested by left ventricular dilation and dysfunction is higher in autosomal dominant Emery-Dreifuss muscular dystrophy than in X-linked Emery-Dreifuss muscular dystrophy (148-151). Emery-Dreifuss muscular dystrophy is known to be associated with two genes; *EMD (STA*), located on chromosome Xq28, which encodes Emerin and *LMNA*, located on chromosome 1q21.2, which encodes Lamins A and C. *EMD* mutations are responsible for X-linked Emery-Dreifuss muscular dystrophy (XL-EDMD) with the majority of mutations being null in nature resulting in complete absence of Emerin expression although variability in the phenotype severity is also observed (152-156). Mutations in *LMNA* cause autosomal dominant EDMD (AD-EDMD) (157) and autosomal recessive EDMD (AR-EDMD) (158).

Diagnosis

Diagnosis of EDMD involves detection of the following triad:

- Early contractures of specific muscles (XL-EDMD – usually before 10 years)
- Slowly progressive wasting and weakness of specific muscles
- Cardiac disease with conduction defects and arrhythmias

Diagnosis of the cardiac elements of EDMD requires an ECG to detect arrhythmias and a cardiac echo to detect dilated cardiomyopathy.

Family history can be used to help distinguish between XL-EDMD, AD-EDMD and AR-EDMD. Alternatively, Emerin immunodetection studies can be used to determine which gene genetic testing is more appropriate for.

Treatment/Management

Treatment of the cardiac elements of EDMD can include pacemaker or defibrillator implantation, anti-arrhythmic drugs and drug therapy for heart failure. In addition, regular cardiac assessment using ECG (1-2 yearly) and echocardiography (1-5 yearly) is recommended. Cardiac evaluation for relatives at risk for AD-EDMD and female carriers of XL-EDMD is also advised.

Dystrophinopathies

Epidemiology

The dystrophinopathies encompass a spectrum of muscle disease disorders including the severe Duchenne muscular dystrophy and the milder Becker muscular dystrophy. Duchenne muscular dystrophy (DMD) (OMIM#310200) is a progressive muscle wasting disease usually first presenting in early childhood with delayed milestones such as delays in sitting and standing independently. Incidence for DMD is estimated in the UK at 1 in 5,618 live male births (159). Most affected children are wheelchair bound by 12 years. Cardiomyopathy is the main cardiovascular complication, found almost universally after age 18 years, and represents one of the major causes of premature death (which tends to occur before

the third decade of life) (111). Becker muscular dystrophy (BMD) (OMIM#300376) is also characterised by progressive muscle wasting but is later-onset and has a more benign course than DMD and loss of the ability to walk may occur late (i.e. 40s or 50s) (45). Incidence for BMD is estimated in the UK at 1 in 18,450 live male births (159). Some affected individuals present with activity-induced cramping, flexion contractures of the elbows, and wheelchair dependency if present is often after the age of 16 years (111). BMD also differentiates from DMD with cases preserving their neck flexor muscle strength. Heart failure from dilated cardiomyopathy is the most common cause of morbidity and death. DMD-related dilated cardiomyopathy usually shows no clinical evidence of skeletal muscle disease (160), is characterised by left ventricular dilation and congestive heart failure and progresses rapidly to death in several years in males with slower progression over a decade or more in females (161).

These disorders are caused by mutations in the dystrophin gene, *DMD*, located on chromosome Xp21 and are inherited in an X-linked recessive pattern (162-165). Large out-of-frame mutations or exon duplications in the *DMD* gene cause approximately 65-70 percent of DMD with the rest caused by mostly nonsense or frameshift mutations resulting in early chain termination (45). Whereas DMD results from the complete or almost complete reduction of dystrophin, BMD is caused by in-frame mutations that result in a partial reduction of dystrophin.

Diagnosis

Diagnosis of a dystrophinopathy is based on clinical signs such as progressive symmetrical muscle weakness. Genetic testing for dystrophin mutations is also clinically available. Echocardiogram and ECG are the key tools for analysing cardiovascular involvement and progression.

DMD

- ECG abnormal >90%, detectable from 6 years old
- ECHO abnormal >90% HCM & DCM
- dysrrhythmia

BMD

- ECG abnormal between 45% (166) and 90% (167)
- ECHO abnormal between 17% DCM (166) and 65% HCM and DCM (167)
- Unrelated to phenotype/severity of MD
- dysrrhythmia

Treatment/Management

Where possible, the dystrophinopathies are treated on a symptomatic basis. Treatment of dilated cardiomyopathy can involve anti-congestive medications, ACE inhibitors and ß-blockers. Regular cardiac surveillance (ECG – 1-2 yearly and ECHO – 1-5 yearly) is also recommended with Holter in symptomatic or abnormal ECG changes, both in affected individuals and in carriers.

Familial Hypercholesterolaemia

Epidemiology

Familial hypercholesterolaemia (FH) (OMIM#143890) is an autosomal dominant disorder caused by mutations that directly affect the rate at which low density lipoprotein cholesterol (LDL-C) is cleared from the blood. The subsequent elevated levels of LDL-C cause accelerated atherosclerosis resulting in increased risk of coronary heart disease (168; 169). Familial hypercholesterolaemia has an estimated prevalence of approximately 1 in 500 (170). The proportion of FH subjects identified and being treated in lipid clinics to date in the UK is, at best, 15% of the predicted number (with the majority of these being older individuals) (171; 172). Since lipid-lowering drug therapy with statins substantially

reduces coronary morbidity and mortality, identification of affected individuals by screening is crucially important.

Since FH is an autosomal dominant disorder the estimated carrier frequency for mutations causing FH is 1 in 500. However, this has never been tested directly. Mutations in at least three distinct loci cause FH (173-175): 1) mutations in the low density lipoprotein receptor gene (*LDLR*) account for the majority of identified mutations; 2) one particular mutation (p.R3527Q) in the gene encoding the ligand for the LDL receptor, namely apolipoprotein B (APOB) occurs in about 5% of UK patients; 3) one common gain of function mutation in the protein convertase subtilisin/kexin type 9 (*PCSK9*) gene, which encodes an enzyme that is involved in degrading the LDLR protein in the lysosome of the cell and preventing it recycling, has been identified in the UK (p.D374Y) and occurs in ~2% of FH patients For the *LDLR* gene, currently over 1000 mutations have been identified world-wide, with more than 100 reported in UK patients to date (174).

The primary outcome of having inherited an FH-causing mutation is elevated levels of LDL-C. However, estimating the penetrance of FH-causing mutations is complicated by the fact that elevated levels of LDL-C also occur commonly in the general population. Thus there is a considerable overlap in plasma LDL-C levels between FH-mutation-positive and normal individuals which has been shown to occur from birth, such that an unequivocal diagnosis of FH cannot be given in 8-19% of children based on lipid levels alone (176). However, the penetrance is high, with essentially all mutation carriers having LDL-C levels above the age and gender population mean. In a study from Denmark (177), 76% of mutation carrier relatives had LDL-C levels above the 90th percentile although 15% of non-mutation carrier relatives also had levels above this cut-off. However, this means that a simple LDL-C measure will not distinguish mutation carriers and non-carriers well. Data from the Dutch data set of over 2000 mutation-positive and negative FH relatives demonstrates that this overlap increases with age, due to the general increase in LDL-C levels seen in normal people as they age, such that by the age of 45-55 years, the false negative rate using the inflexion between the LDL-C distribution in mutation carriers and non-carriers is ~45%. The conclusion from this data is that when a relative has inherited an FH-causing mutation, the penetrance is 100%, although other relatives who have not inherited the family mutation may also have elevated LDL-C for polygenic and environmental reasons (e.g. a poor diet) (178).

Diagnosis

Serum cholesterol concentrations are elevated from birth (generally twice normal values). By adult life, serum cholesterol in heterozygotes is typically 9.0-14.0 mmol/l. Heterozygotes also develop xanthomata over tendons, especially the Achilles tendons and the tendons overlying the knuckles of the hand. Corneal arcus and xanthelasma also tend to develop at a younger age than in the general population. Clinical diagnosis of FH is based on family history of hypercholesterolaemia and premature coronary atherosclerosis, the lipid profile, and the presence of xanthomata.

Treatment/Management

The aim of treatment in FH is directed towards preventing the development and/or progression of coronary heart disease. This is achieved by a combination of LDL lowering and general enhancement of cardiovascular protection. Treatment is usually with statins, which are often started in the late teens in men and later, perhaps after completion of child-bearing, in women. Lifestyle modifications are also important such as a healthy diet and avoiding smoking.

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Appendix 2 Questionnaires sent to ICCS

Review of Genetic Cardiac Services in the UK
Follow-up Questionnaire to lead clinicians
RETURN DATE FRIDAY 7th March 2008

Contact details of individual completing the questionnaire:

Full Name: (including title)	
Name of hospital:	
Corresponding Strategic Health Authority:	
Telephone:	
E-mail:	

Overview of Service:

Please provide an overview of your service. Please attach any documents such as service prospectus, specification, aim or scope of service, commissioning documents.

- Type of service (for example Marfan, Arrhythmia, Cardiomyopathy, inherited congenital heart disease, multi-condition, paediatric multi-condition etc)

- How the service operates

Is it multi-disciplinary, runs parallel genetics and cardiology clinics or stand alone clinics?

- Location

Is the clinic centrally held or a central clinic with satellite clinics?

- Target population

Is it aimed at children, adults or both?

- Other comments

Staffing of Service:

Please provide approximate number of half day sessions per month for the following types of staff supporting the service including time spent on clinical activity and associated administration but not on research projects.

	Number of half day sessions per month	Are the clinic sessions in your job plan? (Y/N)
Consultants (please specify specialism)		
Research Posts (for NHS health care activity only)		
Genetic Counsellors		
Specialist Nurses		
Other Clinicians		
Others such as cardiac physiologists (please specify)		

Activity Information (please provide a best estimate if exact figures are not available)

		Please indicate if an estimate
Number of clinics held per month (in half day sessions)		
Number of the above clinics that are joint clinics and specify the type of professionals involved (eg: cardiologist and geneticist or cardiologist and genetic counsellor)		
Are any of the patients attending for non-genetic conditions? If so what proportion are for non-genetic conditions?		
Number of multi-disciplinary team meetings between cardiology & genetics per month		
Number of new referrals per year (patients not families)		
Number of patients seen per year (patients not families)		
No. of families seen per year (this will include those counted above)		
Number of other patients seen as a result of cascade appointments from index patient (if known)		
Approximate time set aside for each new appointment		
Approximate time set aside for each follow up appointment		
Please list the conditions seen most commonly in your service		

Care Pathways

Who refers patients? **(Paediatrics, muscle clinics, FH, genetics, general cardiology, GP other- please specify)**	
Are there agreed protocols/care pathways for management? If yes **please attach.**	
If no - **are patients routinely followed up by:** • **Specialist condition specific clinic** • **Specialist cardiology clinic** • **Specialist genetics clinic** • **Other service(s) - please specify**	
What pathways do you have for cascading diagnostic information in the family and follow up in your service or another NHS service?	
What relationship do you have with lipid/ FH clinics? Please circle :	**Lipid clinic refers to our service** **Yes/ No/ N/a** **We refer to lipid clinic** **Yes/ No/ N/a** **No relationship** **Yes/ No/ N/a** **Other - please specify:**
Do you have any comments on the effectiveness of care pathways?	

Clinical guidelines and patient information

Please indicate which guidelines are used
Please list patient information used and if you have developed your own information, please send us a copy

Special investigation

Which of the following specialist investigations are available on site at the time of the clinic?

Echocardiogram	**Yes/No**
ECG	**Yes/No**
Specialist ophthalmology testing for Marfan Syndrome	**Yes/No**
Other	**Please specify**
What are the gaps?	

Genetic Testing

Which genetic tests have you requested over the last year? Please complete the table for each type of test with the following information:

Cardiac Genetic Test	**Approxi--mate number requested per year**	**Please list who can request the test - clinical geneticist, genetic counsellor, cardiologist, GP, paediatrician, general pathologist, specialist pathologist, other (please specify). Please list more than one if relevant and state the approximate % of tests requested by the different clinician categories.**
Which clinical group pays for the tests?		
Please describe any gaps in genetic test provision and/ or difficulties in accessing tests		

How are genetic tests requests agreed? (Please tick one or more boxes)

Consultant geneticist acts as a gatekeeper	
Genetic laboratory acts as a gatekeeper	
Test agreed by laboratory on fulfilment of agreed criteria	
Multidisciplinary genetics team acts as a gatekeeper	
Specialist cardiology department agrees test	
Cardiology department agrees test	
PCT agrees test	
No agreement necessary	
Other - please state	

What factors are taken into account in agreeing individual genetic tests (please tick more than 1 box *and rank the 3 most important factors - 1 being most important*)

Fulfilment of formal criteria	
Integration of the test in an agreed care pathway	
Estimate of expected clinical utility in individual cases	
Cost	
The availability of funds in a particular annual budget	
Local availability of the test	
Availability of the test as a UKGTN test	
Test result required for entry into clinical trial	
The involvement of the PCT	
The ability to provide test result in nationally expected timescale	
Other (please specify)	

Assessment of Risk

How is an overall assessment of risk made (including risk of inheriting the condition, long term cardiac morbidity and mortality) and how is it communicated to the patient?

Do you routinely refer patients to support groups? If yes, please state which.

Gaps in services - Please comment on any gaps in services

How is chapter 8 of the NSF being addressed in your region?

Thank you for completing the questionnaire

Follow-up Marfan Questionnaire to lead clinicians
RETURN DATE FRIDAY 15th February 2008

Contact details of individual completing the questionnaire:

Full Name: (including title)	
Name of hospital:	
Corresponding Strategic Health Authority:	
Telephone:	
E-mail:	

Overview of Service:

Please provide an overview of your service. Please attach any documents such as service prospectus, specification, aim or scope of service, commissioning documents.

- Type of service (for example Marfan, Arrhythmia, Cardiomyopathy, inherited congenital heart disease, multi-condition, paediatric multi-condition etc)

- How the service operates

Is it multi-disciplinary, runs parallel genetics and cardiology clinics or stand alone clinics?

- Location

Is the clinic centrally held or a central clinic with satellite clinics?

- Target population

Is it aimed at children, adults or both?

- Other comments

Staffing of Service:

Please provide approximate number of half day sessions per month for the following types of staff supporting the service including time spent on clinical activity and associated administration but not on research projects.

	Number of half day sessions per month	Are the clinic sessions in your job plan? (Y/N)
Consultants (please specify specialism)		
Research Posts (for NHS health care activity only)		
Genetic Counsellors		
Specialist Nurses		
Other Clinicians		
Others such as cardiac physiologists (please specify)		

Activity Information (please provide a best estimate if exact figures are not available)

		Please indicate if an estimate
Number of clinics held per month (in half day sessions)		
Number of the above clinics that are joint clinics and specify the type of professionals involved (eg: cardiologist and geneticist or cardiologist and genetic counsellor)		
Are any of the patients attending for non-genetic conditions? If so what proportion are for non-genetic conditions?		
Number of multi-disciplinary team meetings between cardiology & genetics per month		
Number of new referrals per year (patients not families)		
Number of patients seen per year (patients not families)		
No. of families seen per year (this will include those counted above)		
Number of other patients seen as a result of cascade appointments from index patient (if known)		
Approximate time set aside for each new appointment		
Approximate time set aside for each follow up appointment		
Please list the conditions seen most commonly in your service		

Care Pathways

Who refers patients? **(Paediatrics, muscle clinics, FH, genetics, general cardiology, GP other- please specify)**	
Are there agreed protocols/care pathways for management? If yes **please attach.**	
If no - **are patients routinely followed up by:** • **Specialist condition specific clinic** • **Specialist cardiology clinic** • **Specialist genetics clinic** • **Orthopaedics** • **Ophthalmology** • **Rheumatology and pain clinics** • **Other service(s) - please specify**	
What pathways do you have for cascading diagnostic information in the family and follow up in your service or another NHS service?	
Do you have any comments on the effectiveness of care pathways?	

Clinical guidelines and patient information

Please indicate which guidelines are used
Please list patient information used and if you have developed your own information, please send us a copy

Special investigation

Which of the following specialist investigations are available on site at the time of the clinic?

Echocardiogram	**Yes/No**
ECG	**Yes/No**
Specialist ophthalmology testing for Marfan Syndrome	**Yes/No**
Other	**Please specify**
What are the gaps?	

Genetic Testing

Which genetic tests have you requested over the last year? Please complete the table for each type of test with the following information:

Cardiac Genetic Test	**Approxi--mate number requested per year**	**Please list who can request the test - clinical geneticist, genetic counsellor, cardiologist, GP, paediatrician, general pathologist, specialist pathologist, other (please specify). Please list more than one if relevant and state the approximate % of tests requested by the different clinician categories.**
Which clinical group pays for the tests?		
Please describe any gaps in genetic test provision and/ or difficulties in accessing tests		

How are genetic tests requests agreed? (Please tick one or more boxes)

Consultant geneticist acts as a gatekeeper	
Genetic laboratory acts as a gatekeeper	
Test agreed by laboratory on fulfilment of agreed criteria	
Multidisciplinary genetics team acts as a gatekeeper	
Specialist cardiology department agrees test	
Cardiology department agrees test	
PCT agrees test	
No agreement necessary	
Other - please state	

What factors are taken into account in agreeing individual genetic tests (please tick more than 1 box *and rank the 3 most important factors - 1 being most important*)

Fulfilment of formal criteria	
Integration of the test in an agreed care pathway	
Estimate of expected clinical utility in individual cases	
Cost	
The availability of funds in a particular annual budget	
Local availability of the test	
Availability of the test as a UKGTN test	
Test result required for entry into clinical trial	
The involvement of the PCT	
The ability to provide test result in nationally expected timescale	
Other (please specify)	

Assessment of Risk

How is an overall assessment of risk made (including risk of inheriting the condition, long term cardiac morbidity and mortality) and how is it communicated to the patient?

Do you routinely refer patients to support groups? If yes, please state which.

Gaps in services - Please comment on any gaps in services

How is chapter 8 of the NSF being addressed in your region?

Thank you for completing the questionnaire

Appendix 3 Calculations for estimating shortfall in activity

Best regional provision

Services in the 3 SHAs in England that were provided on a formal regional basis were used to estimate a likely level of provision in terms of annual rate of new patient referral as follows.

SHA	Services	Numbers of new patients	Population (million)
Northeast	Northeast	205	2.6[1]
Yorkshire and Humber	Leeds Sheffield	429 217	5.1
South Central (part)	Oxford	379	3.5[2]
Total		1,230	11.2
Rate	110 patients per million		

1 SHA population used (catchment population quoted as 3 million)
2 Catchment population for this service quoted as 3.5 million (does not include Southampton, Portsmouth and Isle of Wight)

London provision

SHA	Services	Numbers of new patients	Population (million)
London and SE Coast	London LCH	130	
	London Northwick Park	700	
	London Guys, Kings and Lewisham	630	
	London St Georges	419	
	London, THH	523	
Total		2402	11,761
Rate	204.2 patients per million		

Calculations

Analysis of possible shortfall taking the country as a whole (ie including London services), population 60.6 million

1. Using regional 'best rates'

Number of new patients per million = 110
Expected number of new patients in UK = 6,666
Actual number of new patients seen = 5,774
Shortfall = 892

Conclusion: here we assume London services are filling the gap of inadequate services in some regions. Overall services might be adequate if London services are provided to the whole country on an equitable basis.

2. Using London 'best rates'

Number of new patients per million = 204.23
Expected number of new patients in UK = 12,376
Actual number of new patients seen = 5,774
Shortfall over whole country = 6,602

Conclusion: major shortfall – all in regions outside London.

Analysis excluding London and SE (population 48.8 million)

3. Using regional 'best rates'

Expected number of patients = 5,368
Actual patients seen = 3,078
Shortfall over regions = 2,290

Conclusion: some shortfall in regions outside London. However, this estimate is probably low as all regional services report lack of capacity to meet demand.

***4*. Using London 'best rates'**

Expected number of patients = 9,967
Actual patients seen = 3,078
Shortfall in regions = 6,889

Conclusion: major shortfall – all in regions outside London.

Appendix 4 Service Profile of Genetic Tests Listed by UKGTN

Disease (OMIM)	Gene (OMIM)	Listed on UK GTN	Testing Lab	Service Profile
Barth Syndrome; BTHS (302060)	Tafazzin (Cardiomyopathy, Dilated 3a (Xlinked); Endocardial Fibroelastosis 2; Barth Syndrome); Taz (300394)	Y	1	Sequencing of selected exons, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis and postnatal routine diagnosis.
Brugada Syndrome (601144)	Sodium Channel, Voltage-Gated, Type V, Alpha (Long QT Syndrome 3); SCN5A (600163)	Y	2	Mutation scanning and confirmation of known mutation. Prenatal diagnosis, postnatal routine diagnosis and postnatal urgent diagnosis.
Cardiomyopathy Dilated, 1A; CMD1A (115200)	Lamin A/C; LMNA. (150330)	Y	3	Sequencing of entire coding region and confirmation of known mutations. Routine and urgent postnatal diagnosis.
	Myosin Binding Protein C, Cardiac; MYBPC3. (600958)	Y	2	Mutation scanning and confirmation of known mutation. Prenatal diagnosis, routine and urgent postnatal diagnosis.
	Myosin, Heavy Polypeptide 7, Cardiac Muscle, Beta; MYH7 (160760)	Y	2,4*	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis, routine and urgent postnatal diagnosis.
	Troponin T2, Cardiac; TNNT2 (191045)	Y	2,4*	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis, routine and urgent postnatal diagnosis.

Cardiomyopathy Familial Hypertrophic, 2; CMH2 (115195)	Troponin T2, Cardiac; TNNT2 (191045)	Y	4	Mutation scanning and confirmation of known mutation. Prenatal diagnosis, routine and urgent postnatal diagnosis.
Cardiomyopathy Familial Hypertrophic, 4; CMH4 (115197)	Myosin Binding Protein C, Cardiac; MYBPC3 (600958)	Y	4	Mutation scanning and confirmation of known mutation. Prenatal diagnosis, routine and urgent postnatal diagnosis.
Cardiomyopathy Familial Hypertrophic; CMH (192600)	TRNA Leucine 1 (UUA/G); MT-TL1; (590050)	Y	5	Targeted mutation analysis and confirmation of known mutations. Routine postnatal diagnosis
	Myosin Binding Protein C, Cardiac; MYBPC3 (600958)	Y	2,4*	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis, routine and urgent postnatal diagnosis.
	Myosin, Heavy Polypeptide 7, Cardiac Muscle, Beta; MYH7 (160760)	Y	2,4*	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis, routine and urgent postnatal diagnosis.
	Troponin l Type 3 (cardiac) TNNl3 (191044)	Y	2,4*	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis, routine and urgent postnatal diagnosis.
	Troponin T2, Cardiac; TNNT2 (191045)	Y	2,4*	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis, routine and urgent postnatal diagnosis.

CPVT Catecholaminergic Polymorphic Ventricular Tachycardia (604772)	Ryanodine Receptor 2 (cardiac); RYR2 (180902)	Test approved to be added April 2009	11	Sequencing of selected exons, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis and routine post natal diagnosis.
Ehlers Danlos syndrome Type IV (130050)	Collagen type III alpha 1 (Ehlers Danlos type IV, autosomal dominant) COL3A1 (20180)	Y	10	Sequencing of entire coding region, sequencing of selected exons and confirmation of known mutations. Prenatal diagnosis, routine and urgent postnatal diagnosis
Hypercholesterolemia, Autosomal Dominant (143890)	Low Density Lipoprotein Receptor (Familial Hypercholesterolemia); LDLR (606945)	Y	4 6	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Routine postnatal diagnosis. Targeted mutation analysis, confirmation of known mutations and comprehensive analysis. Routine postnatal diagnosis.
Hypercholesterolemia, Autosomal Dominant, Type B (144010)	Apolipoprotein B (Including Ag(X) Antigen); APOB (107730)	Y	4 6	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Routine postnatal diagnosis. Targeted mutation analysis and confirmation of known mutations. Routine postnatal diagnosis.
Long QT Syndrome 1; LQT1 (192500)	Potassium Voltage-Gated Channel, KQT-Like Subfamily, Member 1; KCNQ1 (607542)	Y	2	Mutation scanning andconfirmation of known mutation. Prenatal diagnosis and routine postnatal diagnosis.

Long QT 2 (152427)	Potassium channel, voltage-gated, subfamily 2; KCNH2	Y	2	Sequencing of entire coding region, mutation scanning, confirmation of known mutation and comprehensive analysis. Prenatal diagnosis, routine and urgent postnatal diagnosis.
Long QT Syndrome 3; LQT3 (603830)	Sodium Channel, Voltage-Gated, Type V, Alpha subunit (Long QT Syndrome 3); SCN5A (600163)	Y	2	Mutation scanning and confirmation of known mutation. Prenatal diagnosis and routine postnatal diagnosis.
Long QT 5 (176261)	Potassium channel, voltage-gated ISK-related subfamily. Member 1; KCNE1	Y	2	Sequencing of entire coding region, mutation scanning, confirmation of known mutation and comprehensive analysis. Prenatal diagnosis, routine and urgent postnatal diagnosis.
Long QT syndrome 6 (603796)	Potassium voltage-gated channel ISK-related family member 2, KCNE2	Y	2	Sequencing of entire coding region, mutation scanning, confirmation of known mutation and comprehensive analysis. Prenatal diagnosis, routine and urgent postnatal diagnosis.
Marfan Syndrome; MFS (154700)	Fibrillin 1 (Marfan Syndrome); FBN1 (134797)	Y	5 7 8	Gene tracking. Routine postnatal diagnosis. Mutation scanning and confirmation of known mutations. Prenatal diagnosis and routine postnatal diagnosis. Gene tracking. Prenatal diagnosis and routine postnatal diagnosis.

Marfan Syndrome, Type II; MFS2 (154705)	Transforming growth factor, beta receptor II (70/80kDa); TGFBR2 (190182)	Y	7	Mutation scanning, targeted mutation analysis and confirmation of known mutation. Prenatal diagnosis, routine and urgent postnatal diagnosis.
Noonan Syndrome 1; NS1 (163950)	Protein Tyrosine Phosphatase, Non-receptor Type 11 (Noonan Syndrome 1); PTPN11 (176876)	Y	9	Mutation scanning, targeted mutation analysis and confirmation of known mutations. Prenatal diagnosis, routine and urgent postnatal diagnosis.

1 Bristol Regional Laboratory
2 Oxford Regional Genetics Centre
3 Exeter Regional Genetics Centre
4 London NE Thames Regional Genetics Centre (Great Ormond Street Hospital)
5 West Midlands Inherited Metabolic Disorders
6 Northern Ireland Regional Genetics Centre
7 Wessex Regional Genetics Laboratory
8 Dundee Molecular Genetics Laboratory
9 SW Thames Molecular Genetics Diagnostic Laboratory
10 Sheffield Molecular Genetics Service
11 Manchester Regional Molecular Genetics Laboratory

*When more than one laboratory offers testing for a particular gene there may be differences in the exact service profile offered by each laboratory. Check UKGTN website for details.

Information from the UKGTN website accessed on 15th January 2009.
http://www.genetictestingnetwork.org.uk/gtn

The following genetic tests are also listed on the UKGTN that have cardiac involvement:
Alagille Syndrome (118450)
Emery-dreifuss muscular dystrophy AD (181350)
Emery-dreifuss muscular dystrophy X linked (310300)
Jervell and Lange-Neilsen syndrome (220400)
Muscular dystrophy Limb girdle type 1B (159001)
Other Muscular dystrophies

We have not included congenital heart diseases occurring as part of a syndrome presentation where the condition is almost certain to have occurred by '*de novo*' mutation in the affected child or as a mosaic in the parental gonad for example CHARGE syndrome and chromosome disorders including Down syndrome.

Appendix 5 Members of the Inherited Cardiovascular Conditions Services Working Group

Name	Title and Organization
Corinna Alberg	Project Manager, PHG Foundation, Cambridge
Dr Elijah Behr	Senior Lecturer & Honorary Consultant Cardiologist, Cardiac & Vascular Division, St George's University of London
Dr Ed Blair	Consultant in Clinical Genetics, Department of Clinical Genetics, The Churchill Hospital, Oxford
Dr Paul Brennan	Consultant in Clinical Genetics, Teeside Genetics Unit, James Cook Hospital, Middlesbrough
Dr Hilary Burton	Consultant in Public Health Medicine, PHG Foundation, Cambridge
Dr Steve Cox	Deputy Chief Executive, CRY, Tadworth, Surrey
Genevieve Dalton	Network Director, Anglia Stroke & Heart Network
Dr Perry Elliott	Reader in Inherited Cardiac Disease, The Heart Hospital, University College London
Dr Iain Findlay	Consultant Cardiologist, Royal Alexandra Hospital, Paisley, Scotland
Dr Helen Firth	Consultant in Medical Genetics, Addenbrooke's Hospital NHS Trust, Cambridge
Professor Clifford Garratt	Professor of Cardiology, Manchester Heart Centre, Manchester Royal Infirmary
Dr Martin Goddard	Consultant Histopathologist, Papworth Hospital, Cambridge
Alison Hall	Project Manager (Law & Policy), PHG Foundation, Cambridge
Robert Hall	Chief Executive, Cardiomyopathy Association, Chesham, Bucks
Professor Steve Humphries	BHF Professor of Cardiovascular Genetics, Centre for Cardiovascular Genetics, BHF Laboratories, London
Anne Jolly	Chief Executive, SADS UK
Dr Mike Knapton	Associate Medical Director (Prevention & Care) British Heart Foundation, London
Dr Dhavendra Kumar	Consultant in Clinical Genetics, Institute of Medical Genetics, University Hospital of Wales, Cardiff
Dr Peter Lunt	UKGTN Advisor, St Michael's Hospital, Bristol
Dr Pascal McKeown	Consultant / Senior Lecturer in Cardiology, Centre for Public Health, Queen's University Belfast & Belfast Health & Social Care Trust
Dr Vicky Murday	Consultant, Ferguson Smith Centre for Clinical Genetics, Yorkhill Hospital, Glasgow
Diane Rust	Chairman/Support Co-ordinator, Marfan Association UK, Fleet, Hants
Robin Rust	Marfan Lecturer, Marfan Association UK, Fleet, Hants
Dr Gurdeep Sagoo	Epidemiologist. MRC Biostatistics Unit, Cambridge
Dr Simon Sanderson	Consultant Senior Lecturer, PHG Foundation & Cambridge University
Dr Anneke Seller	Consultant Director of Molecular Genetics Service, Oxford Radcliffe Hospitals NHS Trust, The Churchill Hospital, Oxford
Dr Alison Stewart	Principal Associate, PHG Foundation, Cambridge
Dr Fiona Stewart	Consultant in Clinical Genetics, Belfast City Hospital, Belfast
Dr Graham Stuart	Consultant Cardiologist, Bristol Congenital Cardiac Unit, Bristol Royal Infirmary & Bristol Royal Hospital for Children
Dr Jenny Taylor	Programme Director, Genetics & Pathology Theme, Oxford Biomedical Research Centre
Professor Hugh Watkins	Field Marshal Alexander Professor of Cardiovascular Medicine, Oxford University, John Radcliffe Hospital, Oxford
Jacquie Westwood	Director of Specialised Services SE London, Bexley Care Trust, Bexleyheath, Kent
Mike Yates	National Programme Manager, Arrhythmias & Sudden Cardiac Death, Department of Health, London

Appendix 6 Membership of the Ethical and Legal Subgroup

Name	Profession	Affiliation
Glen Brice (co-opted member)	Genetic Counsellor	St George's Hospital, Department of Cardiological Sciences, London
Dr Helen Firth	Consultant Clinical Geneticist	Cambridge University Hospitals, NHS Trust, Cambridge
Alison Hall	Project Manager (Law and Genetics)	PHG Foundation, Cambridge
Dr Martin Goddard	Consultant Histopathologist and clinical lead for internal education and medical workforce	Papworth Hospitals NHS Foundation Trust, Papworth
Professor Steven Humphries	British Heart Foundation Professor of Cardiovascular Genetics	UCL, Institute of Human Genetics and Health, London
Professor Mike Parker (co-opted member)	Professor of Bioethics and Director of the Ethox Centre	The Ethox Centre, Division of Public Health and Primary Health Care, University of Oxford
Diane Rust	Chairman and Support co-ordinator	The Marfan Association UK
Jenny Taylor	Programme Director	Genomics & Pathology Theme, Oxford Biomedical Research Centre, Wellcome Trust Centre for Human Genetics, University of Oxford (to April 2008)

PHG Foundation
Strangeways Research Laboratory
2 Worts Causeway
Cambridge CB1 8RN

Tel: +44 (0) 1223 740200
Fax: +44 (0) 1223 740892

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