

United Kingdom Haemophilia Centre Doctors' Organisation

Draft for consultation

Clinical Genetics Services For Haemophilia

Address for correspondence

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Preface

This is the second UKHCDO Report on Genetic Services for haemophilia and other hereditary bleeding disorders; the first Working Party under the chairmanship of Professor Ian Peake published its Report in 1997. The current Report has been prepared by a Working Party appointed in 2001. We have been supported by links with clinical genetics services, with the Joint Committee on Medical Genetics, the Department of Health's Genetics Advisory Commissioning Group (GenCAG) and more recently with the newly established UK Genetic Testing Network.

The Report makes substantial recommendations for changes in the provision of both clinical and laboratory haemophilia genetic services. Some of the proposals have been put in place, like the establishment of the UK Haemophilia Genetic Laboratory Network, whilst others will require further discussion before implementation.

The Report's recommendations are in keeping with the recently issued White Paper 'Our inheritance, our future – realising the potential developments in genetic services in the NHS.' In this the government emphasised the need for enhancements in genetic laboratory services, counselling, education and research. To promote these activities the Department of Health is investing £50million over the next 3 years.

Whilst much of this Report principally relates to haemophilia A and B, in the near future we anticipate that the fruits of current research in von Willebrand disease will need to be translated to the NHS genetic laboratories to enable patients and families to benefit from these advances.

I should like to acknowledge the enthusiastic and collaborative way in which members worked speedily to produce this report. We are particularly in debt to those Working Party members representing other organisations for bringing fresh ideas and insights to our deliberations.

We hope you find the Report informative and useful. I would welcome comments and feedback.

Christopher A Ludlam
Chairman

Membership of Working Party

Professor Christopher Ludlam	Chairman
Professor John Pasi	Secretary
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Professor Frank Hill	
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Ms Heather Skirton	Association of Genetic Nurses and Counsellors

Section 1

Introduction

The provision of a clinical and laboratory haemophilia service has always required a high degree of coordination between those with an expertise in blood coagulation and colleagues in a range of other clinical services. This is particularly true in relation to the genetic aspects of haemophilia and other heritable bleeding disorders. The UKHCDO Genetics Working Party has drawn on the experience of Regional Genetic Centres and the Report emphasises the desirability of developing close links with them. The guidelines describe a framework of arrangements for clinical and laboratory haemophilia genetic services which depend upon close collaboration with other specialists to provide a cross-disciplinary, seamless service for patients and their families.

The arrangements and standards for services have been described in circulars from the Departments of Health as well as in the UK Haemophilia Alliance Service Specification. This was devised by representatives of the Haemophilia Society, representing patients, UKHCDO, Haemophilia Nurses Association, Chartered Physiotherapists in haemophilia and social workers, as well as clinical and biomedical scientists working in Haemophilia Centres. The Service Specification has been widely acknowledged as being the standard which patients and families should reasonably expect. In this report the Working Party sets out a series of guidelines based on the Service Specification, which aim to promote good clinical practice and provide standards against which services can be audited.

With recent advances in molecular laboratory techniques it is now possible to give each individual patient and family member very reliable genetic information. To enable this genetic data to be used to ensure both the optimal treatment of the patient with a bleeding disorder and for appropriate reproductive decisions in those who may be carriers, there needs to be established clear and robust framework for systematically acquiring the necessary clinical, personal, family and laboratory information upon which decisions can be made. In this report guidance is offered as to how this information can be collected and recorded as a basis for genetic counselling.

Genetic counselling

For individuals within a family to make decisions in relation to a heritable disorder skilled non-directive counselling must be available. It is important to distinguish between information giving and education, and counselling; the latter enables each individual to reach their own decisions based on all the appropriate information. The way in which such counselling services may be developed and the necessary training and skills of the counsellors are set out in the guideline. This is merely a starting point for the service and further discussions, in the light of experience gained, will inform its future direction.

Confidentiality and clinical records

Genetic testing raises many issues of confidentiality and consent. Some of these are generic to all clinical records and are covered by legislation, e.g. Data Protection Act, whereas others are more specific to genetic testing and relate to an individual's understanding of how their genetic information may be used within the family. There is not always clear and definitive statutory guidance available for every situation but we have tried to offer guidance for the

more common situations based on our understanding of current legislation and good clinical practice. We have recommended the establishment of family genetic files as well as formal genetic family registers in Haemophilia Centres.

Information and Informed Consent

Even before a blood sample is taken for genetic testing it is essential that the individual understands what investigations are proposed and the potential use to which the result may be put. To help inform patients and family members a Patient Information Leaflet has been developed which sets out some of the background to genetic testing. It can be used as one of the starting points for counselling. A small audit we have undertaken suggests that many have found it helpful. It is accompanied by a Consent Form that can act as a record of the individual's agreement as to who should receive the result and where data can be held. These are generic forms and for good Clinical Governance it is appropriate to ensure that they conform to local arrangements, in some instances it may also be necessary for an individual to sign a local hospital consent form.

Carriers of haemophilia

The arrangements should be available for haemophilia carriers have been described in detail in the guideline. The counselling of potential carriers should take place at an appropriate time and preferably before pregnancy. The management of early pregnancy requires close collaboration between haemophilia physician and obstetrician and in the case of antenatal diagnosis with a clinical geneticist. The overall arrangements for antenatal diagnosis require a coordinated input from many members of the haemophilia team including the genetic counsellor. The management of the mother and fetus in later pregnancy in relation to any potential haemorrhagic disorder, e.g. carrier of haemophilia, is not covered in this Report.

Genetic testing of children

Children have particular rights in relation to genetic testing. We have addressed some of these in the specific guideline on the value of genetic testing in children and it seeks to inform parents and healthcare staff about some of the important issues related to a child's rights.

Haemophilia Genetic Laboratory Network

The essential cornerstone of a clinical genetic service is a high quality laboratory service. The Working Party has established the UK Haemophilia Genetic Laboratory Network (UKHGLN) which is a consortium of laboratories, mostly within Comprehensive Care Haemophilia Centres, which work to agreed standards of quality and turn round times. A Network national co-ordinating committee oversees collaboration, adherence to quality standards and the development of the service. The UKHGLN is represented on the UK Clinical Genetics Laboratory Network that was recently established by the DOH Genetics Commissioning Advisory Group (GenCAG). This ensures close collaboration between haemophilia genetic services and the wider world of clinical genetics. For the laboratory service to be used appropriately and optimally there needs to be effective collaboration between clinical scientists and clinicians and the guideline offers suggestions on how this can be achieved. A directory of laboratories in the UKHGLN is included which also lists those with particular expertise for some of the rarer hereditary disorders. To make it readily

available the directory has been posted on the web (www.haemophiliaalliance.org.uk/) and will be regularly updated.

Resource

Implementation of the recommendations of this Report will require additional resources to be invested in haemophilia services. The family files and genetic registers will need to be established to record both factual genetic information and details of clinical consultations with patients and family members. Much of this could be developed with the expertise genetic counsellors who will bring experience of arrangements from clinical genetics centres. The financing of the laboratory genetic service needs to be from NHS sources and not dependent on research funding for the core staff, equipment and consumables.

Levels of evidence

Most current guidelines support recommendations with levels of evidence. As there is a paucity of randomised trials for the topics covered in this Report, the recommendations are considered to represent, by common consent, good clinical practise. Some aspects, however, of the guidance have statutory authority, e.g. the handling of data.

Future

Nothing in medicine moves faster than developments in genetics! Although the Report offers current guidance on how services should develop for people with haemophilia and their families, arrangements will need to evolve in response to advances in laboratory techniques, new statutes, changes in the way health services are commissioned, and above all by changes within society and its expectations.

Section 2

The provision of genetic counselling services for haemophilia and related inherited bleeding conditions

Setting the scene

The National Service Specification for Haemophilia and Related Conditions states that all individuals with haemophilia (or a related bleeding disorder) and their families should have access to specialised genetic services. Genetic counselling should be available for all people potentially affected by or at risk of being a carrier of one of these conditions before, during and after the process of genetic analysis (Haemophilia Alliance, 2001). This document sets out proposals for the future direction of genetic counselling provision in haemophilia services.

The current provision of genetic counselling within haemophilia centres varies even within Comprehensive Care Centres. The involvement of different members of staff in genetic counselling depends upon their role within the multidisciplinary team, and the skills, knowledge, experience and qualifications held and used by individual members of the team. Centre teams tend to vary in their membership of professionals from social and psychological services, and in the extent to which these practitioners are explicitly involved in genetic counselling.

All specialist medical and nursing staff within haemophilia centres provide information to patients and families on the following:

- Inheritance patterns
- The nature and implications of inherited bleeding conditions
- Treatment and complications
- The options open to family members who may wish to have genetic testing.

Information on genetic testing and interpretation of results is primarily imparted to patients by haemophilia doctors. Specialist nurses know patients and families well and therefore have an important role in identifying and reaching individuals who may require genetic testing.

The audit of Comprehensive Care Centres does incorporate the genetic service but does not formally examine the quality of counselling or the competency of involved personnel. In this document the UKHCDO and the RCN HNA address the governance issues relating to genetic counselling provision within haemophilia centres. This requires the development of a clear, structured and more formalised approach to the audit of genetic counselling conducted within haemophilia centres.

Whilst many health professionals use counselling skills in their work, genetic counselling is a specialised area of practice with a professional registration system in operation (www.agnc.org.uk/Registration/registration.htm). Essential competencies for genetic counselling practice have been defined by the Association of Genetic Nurses and Counsellors (AGNC), see [Appendix I](#).

Preparing for the future

In the age of molecular genetics, families have greater options for diagnostic, carrier and prenatal testing, and pre-implantation genetic diagnosis. The service provided by Haemophilia Centres has to respond to these developments and the expectations they generate. It is unlikely that all the requirements of the genetic counselling process can be delivered by one individual professional. Different levels and depths of genetic counselling can be provided which address different issues (Miller, 2002). There are differences between the knowledge and skills required to offer a comprehensive haemophilia service and those required for specialist genetic counselling. Families making reproductive decisions need access to all these areas of expertise. Haemophilia Centre staff have the knowledge of current treatment and implications of the condition. However, there may be issues that may need to be considered away from the day to day treatment setting.

Precedents have been set in services for many other types of genetic conditions, where specialist health care and specialist genetic counselling are offered in different settings or by different professionals. For example, patients affected by cystic fibrosis are cared for in specialist centres, but genetic counselling is usually offered to such families by separate specialist genetic staff. Similarly, pregnant clients seeking genetic information about a potential or actual fetal abnormality are referred to genetic services by the obstetric team responsible for management of the pregnancy. In many regional cases, joint clinics are held between genetic services and other specialists to serve the needs of families concerned about conditions affecting a particular body system (e.g joint genetics/ophthalmic clinic, genetic/skeletal dysplasia clinic, genetic/neuromuscular clinic). This enables families to discuss therapeutic options, prognosis for the condition and current reproductive options.

It is essential that those seeking genetic counselling feel free to make decisions that are not constrained by their commitment to existing family members. This professional issue has been identified recently in other areas of healthcare, such as midwifery (Cignacco, 2002) and is of particular importance when considering the ethical principles of autonomy and justice (see [Appendix II](#)). The criteria for offering prenatal genetic testing to individuals include obtaining prior informed consent and confidentiality (Maddox, 1992), and these criteria are more effectively fulfilled when a distinction is made between professionals offering management for a condition and those who offer genetic testing. In particular, genetic test results should be known only to the individuals concerned and the person providing the test (Campbell et al, 1997). Haemophilia specialists are highly committed to the success of treatment and may, or may not, be conscious of the potential impact of this on their ability to remain 'neutral' in the genetic counselling situation. It is also important to consider whether particularly sensitive issues such as paternity can be addressed in a setting where staff and families know each other well. For these reasons families should have access to a genetic counsellor who is not directly involved in provision of care for the affected family, and a choice of venue for receiving genetic counselling, either within or outside their haemophilia centre. Reports by the Genetic Interest Group (2000) have indicated that families should be offered prenatal testing so that they can make decisions relevant to their own situations.

It is not feasible, or necessarily desirable, for all haemophilia specialists to attain the level of practice required for registration as a genetic counsellor, as their work with one group of conditions would not confer generic skills. However, there may be some haemophilia nurses who have a special interest in this area who wish to develop competency to the registration level. This would entail accepting a greater proportion of genetic counselling work and

therefore impact on the skill-mix and responsibilities within the haemophilia team. Becoming a registered genetic counsellor also requires knowledge of a wider range of genetic conditions and therefore a period of time working in the regional genetics centre. Strong links with the Regional Genetics Centre would be necessary along with clinical supervision by a registered genetic counsellor.

Recommendations

The UKHCDO and RCN HNA propose the following developments:

- *Creation of stronger links between haemophilia centres and regional genetics services.*
- *Education and competency development for haemophilia specialists involved in provision of genetic counselling.*

It is proposed that both these areas could be addressed by developing a new role for a specialist registered genetic counsellor in haemophilia and inherited bleeding conditions. This genetic counsellor would work in two settings, the haemophilia centre and the regional genetics service, and with both staff teams. The responsibilities would encompass:

- *Provision of genetic counselling for haemophilia and related inherited bleeding conditions on a sessional basis.*
- *Maintenance of a register of families affected by or at risk of inherited bleeding disorders to enable the haemophilia centre to offer a full service to family members of reproductive age.*
- *Clinical supervision for haemophilia centre staff on genetic counselling issues.*
- *Development of education and training for haemophilia centre staff on genetic issues.*

Contributing to the formulation and evaluation of a competency framework for haemophilia centre staff in the provision of genetic information. This framework would be based on the AGNC competencies but incorporate different levels appropriate for staff working within a specialist area who are not seeking full registration as genetic counsellors. For haemophilia nurses, this would be a logical extension to the existing competency framework published by the RCN HNA (RCN, 2002).

Practical issues

The following models could be considered on a centre-by-centre basis:

Option A: Genetic counsellor is attached to the haemophilia centre

Employment of a specialist genetic nurse who works within the CCC on a sessional basis. The specialist genetic nurse would be mainly based within the Regional Genetic Centre, to enable him or her to access support, supervision and maintain current genetics knowledge. Specialist training in relevant aspects of the management of inherited bleeding disorders would be mandatory, as would regular education and supervision from haemophilia centre staff. An appropriate portion of the salary would be funded by the CCC. This model would be particularly useful for smaller centres. Clients would have the opportunity to consult the nurse specialist in either the genetics or the haemophilia centre.

Option B: Haemophilia specialist nurse registers as genetic counsellor

Identification of a haemophilia nurse specialist with special interest in genetics who changes their role within the Centre and undertakes full registration as a genetic counsellor. The haemophilia nurse would have strong links with staff of the regional genetics centre, for education, supervision and support, and would be expected to regularly spend time in the genetics centre e.g. one day per week. Initially a period of training in the Regional Genetics Centre would be required. Again it is important that clients have the choice of seeing the nurse specialist in either the genetics or the haemophilia centre.

In both of the above cases, the emphasis is on providing strong links between genetics centre and haemophilia centre, and enabling the nurse to access education and supervision in both areas. The system would also enable registers to be kept up to date and enable new developments to be available for families rapidly.

It is suggested that a named clinical geneticist be asked to act as the key link person from a clinical genetics perspective in each region.

Support for a scheme to train and employ genetic counsellors for the field of haemophilia and haemostasis will be sought from the Genetics Commissioning Advisory Group (GenCAG), the Joint Committee for Medical Genetics and the Association of Genetic Nurses and Counsellors.

Section 3

Consent and Written Information

Introduction

Seeking informed consent for genetic testing requires careful and considered explanation. The recommendations of the European Society of Human Genetics (www.eshg.org/) state that genetic testing should be based on respect for the principle of self-determination of the persons concerned and therefore subject to their express, free and informed consent. No condition should be attached to the acceptance or the undertaking of genetic tests. Written informed consent is also required for all types of DNA banking. These recommendations advocate careful consideration of the psychological complexities of testing and a multidisciplinary approach.

Informed consent for testing is conducted in the wider context of genetic counselling. Some key elements related to testing should be considered as part of the content of pre-test discussion and follow-up.

PROCESS

- Establish that a bleeding disorder is present in the family and determine its type and severity
- Establish a pedigree/family tree
- Assess understanding, expectations, beliefs and wishes.
- Acknowledge the implications of individual and family experiences, values and culture.
- Address personal and relationship concerns related to testing
- Provide the opportunity for questions to be asked
- Provide the opportunity for the consultand to present their understanding of the information that has been discussed and its implications for themselves and others.
- Ensure information and its significance is understood and accepted
- Offer a follow-up appointment
- Where the need for ongoing support is identified in the course of the consultation, make appropriate referrals.
- Make clear arrangements for imparting the results of testing

INFORMATION

- The potential clinical effects of being a carrier or affected person
 - Current treatment and implications of the condition
 - The mode of inheritance and the individual's genetic risk.
 - The rationale for identifying the genetic defect
 - The means by which carrier status is assessed
 - What is involved in genetic testing: sample collection; transfer/storage of data; research projects on stored material; insurance issues; risk of error.
 - Information on the procedures for antenatal testing.
- Written information - the NHS consent policy and generic forms point to the importance of making written information available to patients to back up the content

of face to face discussion. NHS organisations remain responsible for satisfying themselves as to the quality and accuracy of the information they provide to patients (see www.doh.gov.uk/consent/hsc2001023.htm, HSC 2001/023 Good Practice in Consent).

Within the context of testing for a bleeding disorder a model information sheet and consent form is given in [Appendix III](#).

Section 4

Data collection, retrieval, storage and disclosure

This document provides a detailed background to data collection and storage and consent/right of access to medical records.

Genetic counselling is an essential part of the comprehensive service offered to patients and their families with haemophilia and other inherited coagulation disorders. It is recognised that this should include the offer of counselling and risk assessment to female relatives at an appropriate age and time in those families with X-linked disorders such as haemophilia. Indeed, the Genetic Interest Group (GIG), an umbrella organisation of genetic disorder support groups states in its document "Guidelines for Genetic Services" (1998) that, '**systems are needed to facilitate efficient, effective, long-term follow up of service users and their families and contact of at-risk relatives.**' In terms of specific recommendations, the same GIG document states that 'the service should enable children and young people in a family to be offered the opportunity of referral for genetic information and counselling when appropriate' and that 'services should make direct contact with young adults in affected families when they reach the age of 16, and invite them to use the service'.

In order to enable this process, clinical genetic services have established a system of family genetic records and genetic family registers.

Family genetic records

The current position in many Haemophilia Centres is almost certainly inadequate. Pedigrees may be compiled but are filed either in the index patient's case notes or manually elsewhere in the Haemophilia Centre.

It is recommended that Haemophilia Centres develop family genetic records of patients with haemophilia and other inherited bleeding disorders.

It is recommended that these notes should

- ***be a separate 'genetic' file***
- ***be kept within the Haemophilia Centre***
- ***contain the family pedigree. The pedigree should be compiled in a standardised way for all haemophilia families using the conventions outlined in 'Guidelines for Pedigree Drawing'(see www.bshg.org.uk/).***
- ***contain the results of all relevant genetic tests, whether biochemical, haematological, cytogenetic or molecular genetic tests.***
- ***contain informed written consent for genetic studies, sharing of appropriate family information and inclusion on a register.***
- ***contain copies of all pedigree related correspondence***
- ***be kept confidential and only accessed by authorised staff of the Haemophilia Centre***

Genetic Family Registers

The maintenance of pedigrees will require continued commitment. It is difficult to be sure that the pedigrees are updated adequately, and a system needs to be in place to offer follow-

up of possibly affected relatives, in particular for the recall and counselling of potential female carriers within haemophilia families.

In conjunction with the development of the family genetic records, it is recommended that a haemophilia genetic register system is also established in each centre.

In simple terms, a genetic register comprises a list of people affected by, or at risk of genetic disease, linked as families, and linked to a diagnostic index (Dean et al. 2000). Such a confidential database of families can serve several functions:

- It can allow regular contact with families,
- Allow planned follow-up in order to offer counselling to at-risk family members at appropriate ages
- Allow recall of families in the light of genetic research developments.

It is usual for such databases to be computerised. Whilst the follow-up and offer of genetic counselling to family members can be reviewed and planned at an annual clinic assessment of the index patient, a computerised register system is a more efficient means of storing and retrieving data, though means of safeguarding confidentiality must be in place.

It has been common practice within clinical genetic services to also include on the genetic register those relevant family members who are included on the pedigree (with their documented relationships) but who have not attended the genetic counselling clinic. Such family members might include the younger sisters of affected male haemophilia patients who should be offered genetic counselling at an appropriate age. The issues of storing such data in respect of the Data Protection Act are outlined below in the section on consent for storage of data.

There is a strong argument therefore to establish, in addition to genetic files, a computerised family register in each Haemophilia Centre whereby:

- Pedigrees are recorded in computerised format – an electronic picture and filing system for family members identified by name, pedigree number and generation; this makes it easier to access and to modify as additional members are added to the family. Some commercial programs are available for this e.g. Cyrillic (based in Oxford UK) and Progeny (USA) though many genetic centres use in-house systems. These programmes contain more facilities than would generally be required within Haemophilia Centres. Presently there is no facility for pedigree information in the UKHCDO database.
- The data recorded on each individual on the register should include:
 1. Standard information (RCP, Clinical Genetic Services, Report 1998)
 - a. Pedigree/family file number
 - b. Surname, first name, sex, date of birth, address
 - c. GP and referring clinician (if a haematologist or paediatrician outside the comprehensive care centre)
 - d. Specific diagnosis (e.g. haemophilia A, haemophilia B, von Willebrand disease etc. etc.).
 2. Test results – including the mutation, if known
 3. Agreed plans for follow-up of patients and of relatives at risk.

Any computerised database is ideally interfaced to a system that can automatically generate follow up letters at appropriate times for girls as they reach an age where genetic counselling can begin. The system would allow cross-referencing between different family members.

The pedigree should be updated at least annually, taking advantage of one of the regular clinic visits of the index patient where possible. At these updates it is important to try and confirm the family relationships that have previously been documented and to add new family members that have been born in the intervening period. Reminders should be put in place to ensure this happens.

Contacting relatives to offer genetic counselling

When a pedigree is taken for the first time or when it is updated, the genetic counsellor will seek to identify those other family members to whom the offer of genetic counselling would be appropriate, such as the close female relatives of a male with haemophilia. It is the usual practice in clinical genetic departments to indicate to the patient (or their parents in the case of a child) those relatives to whom this offer would be appropriate. It is usually regarded as the family's responsibility to contact these relatives and alert them to this offer. The Nuffield Council on Bioethics report in 1993 stated that the primary responsibility for communicating genetic information to a family member lies with the individual and not with the doctor. The Medical Ethics committee of the BMA suggested that in those cases where the individual is unwilling to transmit the information but gives consent for the information to be shared, the genetic centre should approach the relatives through their GP.

Clinical genetic departments often provide the family with an explanatory letter that could be sent to relatives. Certainly it is considered good practice to write to all families following a genetic counselling appointment to provide written confirmation of the risk assessment given during counselling and a summary of the options open to the family, including the possibility of antenatal diagnosis where appropriate.

It is recommended that a post consultation letter is sent to all families indicating the genetic risks, options available and the offer of genetic counselling to other at-risk relatives. The letter should include a recommendation to contact the haemophilia/genetic centre in the event of a pregnancy, preferably as soon as a pregnancy is confirmed.

Issues of consent and confidentiality in genetic counselling

1. Storage of data

With regard to the storage of data, the Human Genetics Commission (HGC) in their report "Inside Information" (section 4.2, page 69) note that the storage of information about other persons raises potential data protection issues. The report states, "there is potentially a considerable amount of information about family members on most medical records. However there is potentially far more significant information on records held by clinical genetic centres. This is especially true when family pedigrees are stored in combined files or where genetic registers are held".

When families are seen in clinic they can be asked to consent for their data, including DNA results, to be stored on a local register and also on the National Register and this is covered in

the information sheet and consent form for molecular genetic analysis and the leaflet explaining the National Haemophilia Database.

Consent to information storage is governed by the Data Protection Act and the common law of confidentiality. The data protection act covers information processing, which is a wide term that includes collection, storage, disclosure, retrieval, destruction and alteration. Schedule 1 of the Act states that personal data shall be processed fairly and lawfully and shall not be processed in the case of sensitive personal data unless at least one of the conditions in schedule 3 is met. Sensitive personal data cover a number of personal details including physical or mental health or condition. Section 8 of schedule 3 states that the processing can take place if it is necessary for medical purposes and is undertaken by

- a health professional
- a person who in the circumstances owes a duty of confidentiality which is equivalent to that which would arise if that person were a Health Professional.

Medical purposes include the purposes of preventative medicine, medical diagnosis, medical research, the provision of care and treatment and the management of health-care services.

There are potential issues for Genetics/Haematology Departments regarding the family tree. The Department of Health white paper “Our Inheritance, Our Future” states (in paragraphs 6.27 and 6.28) that, “under the Data Protection Act, a doctor or counsellor is required to tell relatives that information about them is recorded in the patient’s medical records. Not only is this potentially very bureaucratic, it could also reduce the amount of clinically useful information that doctors feel they are allowed to record. The HGC also said it was possible in some cases that a relative may wish to stop the information about them being recorded. The patient’s interests would then have to be balanced against those of the relative. The government have taken note of the comments made by the HGC and of other concerns about the application of the Data Protection Act to medical record-keeping and established the Health Records and Data Protection Review Group to examine the matter in detail”. This group are due to report in 2003. It is important to recognise that those providing genetic counselling need information about other family members to advise the person who is being seen and to enable provision of accurate information for other family members who may seek advice in the future.

2. Access to records of a relative

There are several issues for Haemophilia Centres in terms not only of the collection and storage of data for genetic counselling but also in the disclosure of clinical details and genetic test results.

Whilst referral of a patient implicitly includes consent to review their medical records, there may be occasions when in the genetic counselling of a family, it is important to have access to the records or test results from relatives.

Examples include

- A woman is referred for carrier testing because she has a male relative with haemophilia – that male relative’s records and test results may need to be accessed.

- A history is obtained that the mother of a boy with haemophilia had a male relative with a bleeding tendency. It may be important to try and obtain details of this relative to see whether there was evidence of a bleeding disorder, and if so, which one. Sometimes the relatives may be deceased.

Under these circumstances, information could be obtained from the patient's case notes. In terms of seeking information from case notes the legal position for living relatives is broadly that consent can be obtained for access to information from that person.

If the person is alive it is recommended that consent is from them or the person with parental responsibility to access the required information

Access to the health records of the deceased is governed by the Access to Health Records Act 1990. This Act applies only to records compiled on or after 1 November 1991, although the record holder (usually an NHS Trust) does have discretion to permit access to earlier records.

The record holder has the right to deny or restrict access if it is felt that disclosure would cause serious harm to the physical or mental health of any other person. Additionally if the patient expressed a wish that all or part of their health record was to remain confidential then these wishes should be respected.

Rights of access to the notes of a person who is no longer alive is unclear. Some hospitals will only allow access if there is consent from the next of kin. In the past advice from the Medical Defense Union and Medical Protection Society has been to permit access only if there is consent from next of kin or a "best friend". The term "next of kin" is used in legislation covering succession and inheritance but currently does not have legal significance in the context of access to information.

It is unclear what a Health Professional should do if there is no longer a personal representative due to the length of time elapsing between death and a request to see the medical records. The common law duty of confidence does apply to the deceased. However unless there is good reason to believe the deceased would have refused access then the public interest regarding the relatives over-rides the principle of duty of confidence to the deceased. A "good reason" in this context would be that the deceased stated that he/she did not want relatives seeing the notes after his/her death.

The needs of the living should be recognised and current legislation should be interpreted by Trusts to reflect this. It is good practice for Trusts to release notes of a deceased person if consent is obtained from a close relative for whom the information is relevant unless the deceased person had specifically refused this. Request for information from medical records should state that the request is being made because the information sought is necessary for the care of a patient. The argument can be advanced that the NHS is a mutual service and therefore a charge should not be made.

3. Disclosure of information about a relative without consent

The above discussion was centered on obtaining information about relatives from medical notes. It is also possible to gain information from colleagues. Although there are many trusted links between departments and laboratories, the established links do not remove the need for consent for both information and sample sharing. However in the case say of a prenatal

diagnosis where there is urgency to share information or samples it should be acceptable under current GMC guidelines to proceed without consent if necessary. An example of such exceptional circumstances would be the case of a pregnant woman presenting at an antenatal clinic and stating that her sister who lives elsewhere is a carrier for haemophilia. If the sister cannot be contacted then, in such circumstances, it should be professionally acceptable for the laboratory that established the diagnosis to share information/samples with those involved in the care of the pregnant woman. The reasons for doing so should be carefully documented.

Disclosure without consent should be carefully considered and documented including the reasons for disclosure and the absence of consent.

Another situation considered by the Human Genetics Commission in their report “Inside Information” is the situation where a relative refuses to consent to the release of important information. The report (section 3.68, page 64) took the view that, “bearing in mind the principle of genetic solidarity and altruism, we take the view that disclosure of sensitive personal genetic information for the benefit of family members in certain circumstances may occasionally be justified. This would arise where a patient refuses to consent to such disclosure and the benefit of disclosure substantially outweighs the patient’s claim to confidentiality”. The Department of Health white paper “Our Inheritance, Our Future” (in section 6.26) supports the principles argued by the HGC, “especially the balancing of respect for individual rights with the need for genetic solidarity and altruism so that genetic knowledge can be shared to help others and society”.

Consent for sharing of information with relatives could be achieved prospectively if such information sharing was discussed at the outset of a genetic consultation and consented to. If this is not the case then it is good practice to try to obtain consent retrospectively if this becomes possible e.g. in this example above, if the carrier sister had been abroad.

In order to avoid these difficulties the working party recommends the use of an information sheet with written consent for genetic testing. The consent obtained includes the agreement for sharing the results of genetic tests for the benefit of other family members.

It is good practice to obtain consent for this disclosure whether the other family members are being seen in the same department or another one.

It is good practice to ensure that the proband both understands the benefit of keeping the primary Health Care Team informed as well as the potential implications of a genetic diagnosis. As mentioned earlier it is recommended that the proband gives consent to information sharing with other Health Professionals.

Section 5

Guidelines for the management of early pregnancy and antenatal diagnosis

It is good practice to address issues related to the genetics of inherited bleeding disorders before the first pregnancy so that individuals and families are not faced with large amounts of information and potentially difficult decisions in a short period of time during early pregnancy. In addition, laboratories should not be asked to provide results under time pressure if this can be avoided. It is the case, however, that some known or potential carriers of bleeding disorders unavoidably present during pregnancy and in these cases the relevant issues must be addressed urgently.

Communication

Good communication between all interested parties is essential to a successful process. This is best co-ordinated by the Haemophilia Centre. Communication should include the pregnant woman, obstetric/foetal medicine unit, laboratories and GP. There may be more than one laboratory involved in providing phenotypic testing, karyotype analysis and molecular diagnosis.

Confirmation of diagnosis

The family diagnosis should be confirmed unequivocally and if necessary affected family members should be reinvestigated. This may be particularly relevant if a diagnosis was made some years ago as reinvestigation with modern techniques and assays may yield important information relevant to genetic counselling and management. The coagulation factor level in the family should be confirmed. A definitive confirmation of the family diagnosis and coagulation factor level may not be possible if an affected family member is not available for investigation. The available phenotypic and genetic laboratory data should be critically reviewed. The quality of results should be reviewed with regard to the techniques and controls used.

A family tree should be drawn up or the accuracy of an existing family tree confirmed. The status of the pregnant woman can then be confirmed.

If the family is affected by a recessive disorder testing of the partner may be helpful.

The diagnosis, coagulation factor level and mutation within the family should be definitively confirmed, if possible, and the family tree updated to ensure that genetic counselling is accurate.

Counselling

If possible genetic counselling should be performed before pregnancy. If this is not possible then genetic counselling should take place as early as possible in the pregnancy. The genetic counselling should be performed in a confidential and comfortable environment by staff who are competent in genetic counselling and knowledgeable about inherited bleeding disorders. In practice this is often a Haemophilia Centre doctor or nurse. Genetic counselling can also be provided by a medical genetics department, in which case there should be close liaison with

the Haemophilia Centre. If antenatal diagnosis is being considered, appropriate staff from the antenatal diagnostic unit should be involved at an early stage.

Genetic counselling should cover the following topics:

Clinical phenotype: The bleeding disorder in the family should be described along with likely bleeding phenotype, potential complications and expected quality of life of affected children and effects of an affected child on the family. It may be necessary to explore the individual's previous experiences of the disorder within the family, particularly in relation to infective complications and severe disability and to describe the impact currently available treatment will have. The treatment efficacy, safety and side effects should be covered. Partners and individuals who have limited first hand experience of the disorder are likely to require extensive counselling about these issues.

Inheritance: The mode of inheritance of the disorder should be described and the situation of the individual seeking counselling established.

Options: The available reproductive options should be discussed. These would include taking no action and accepting the outcome of a pregnancy or, for couples who do not want to have an affected child, options include not having children, adoption, the use of donor gametes, antenatal diagnosis and termination of an affected foetus and preimplantation sexing or diagnosis. The procedures should be explained including how and where they would be performed, their availability, accuracy and success rates and potential risks to foetus and mother. The advantages and disadvantages of each option should be explored including the psychological affects on other family members and the family as whole. These discussions will be affected by the individual's and the family's previous experiences of the disease and its complications.

Antenatal diagnosis

Counselling: Counselling regarding antenatal diagnosis should cover all options available to the pregnant woman and, if appropriate her partner, and the risks and benefits of each approach should be discussed and compared. Options include continuing with the pregnancy, CVS, amniocentesis and cord blood sampling.

Pre-test counselling is given by a combination of appropriate Haemophilia Centre and fetal medicine staff. The individual should be informed about the procedures; how they will be performed, the possibility of not obtaining an adequate sample, non-diagnostic results and potential side effects for both mother and foetus. It should be agreed with the couple what tests will be performed and in what order. In particular it should be agreed whether tests unrelated to the bleeding disorder will be performed. It would be routine practice in most centres to offer karyotype testing, for example. An indication should be given about how long the tests will take to be performed. A crucial part of pretest counselling is a discussion of what options would be taken by the woman with each possible test outcome and the potential effects of these decisions should be explored.

The haemostatic cover for the procedure, if required, should be discussed along with issues related to maternal and foetal exposure to blood products if relevant.

Counselling for antenatal diagnosis should be performed by a combination of haemophilia centre and fetal medicine staff.

Communication of results: It should be agreed in advance who, how and where the results of the antenatal diagnosis tests will be given. Once the results are known the options available to the woman should be discussed. It may be necessary to allow time for the results to be considered before a decision is reached.

Chorion villus sample

Chorion villus sampling (CVS) involves taking a sample of chorionic villi for analysis. The main advantages are that; it allows first trimester diagnosis and so avoids late termination and chorionic villi are a reliable source of foetal DNA. There are no recognised guidelines relating to CVS.

Procedure: Written informed consent for the procedure must be taken.

Before the day of the procedure the mother is scanned to confirm viability of the pregnancy, gestation, number of foetuses and placental site. The procedure takes about 15 minutes and is performed under local anaesthetic by a clinician. On the day of the procedure the viability of the pregnancy is confirmed by ultrasound. Most centres use a transabdominal approach under continuous ultrasound control. This technique is used optimally between 10-11 weeks to allow a first trimester termination but may be used up to 14 weeks gestation. The sample is usually taken using either by single needle aspiration, double needle aspiration using either high-power suction or syringe suction. A transcervical route through a speculum may also be used but is associated with a higher risk of infection related miscarriage and can only be performed up to about 12 weeks gestation. The material obtained is examined microscopically to confirm that it is adequate. The sample is placed in transport medium. The foetal heart is checked after the procedure and Anti-D given if appropriate.

In multiple pregnancies the chorionicity should be established on ultrasound at 10-14 weeks. For dichorionic twins samples are taken from each placenta and labelled with reference to placental site. For monochorionic twins amniocentesis may be preferred as there is not a 100% correlation between chorionicity and zygosity.

Some women may need haemostatic cover, such as DDAVP or recombinant coagulation factor concentrates, for the procedure depending on their diagnosis and level of coagulation factor.

Before leaving, arrangements should be made regarding the method of communication of the result.

Adverse events: The main adverse event related to CVS is miscarriage which is estimated at about 1-2% with an experienced operator. Foetal limb abnormality has been associated with CVS taken before 10 weeks gestation thus most are carried out from 10 weeks gestation (Firth et al 1991). The woman should be warned that she may experience either discomfort or pain during the procedure. Systems should be in place to ensure adequate labelling and handling of the sample.

Laboratory testing: In the case of X-linked disorders the foetal sexing should be established initially. If the foetus is female no further tests are done apart from exclusion of maternal contamination. If the foetus is male tests are performed to establish whether the affected gene has been inherited. This may be done by direct mutation analysis, gene tracking techniques or a combination. Laboratories should be CPA accredited and part of the UK haemophilia genetics laboratory network.

For antenatal diagnosis, procedures and communication between Haemophilia Centre, foetal medicine department, laboratories and GP should be formalised in a written protocol.

Amniocentesis

Cells for karyotyping and as a source of DNA can also be obtained from amniotic fluid. This method carries a lower miscarriage risk and so is preferred to CVS after 15 weeks gestation. The miscarriage rate is about 0.5-1% with skilled operators. The main disadvantage of amniocentesis compared to CVS is that a termination, if necessary, will occur later in pregnancy and a surgical procedure would not be an option in most NHS hospitals. The main advantages are that the miscarriage rate is lower. Amniocentesis can be performed after 14 weeks gestation. A RCOG guideline for amniocentesis is available (1).

Procedure: Haemophilia Centres should make arrangements for amniocentesis to be performed in a specialist centre that complies with RCOG guidelines (1).

Written informed consent for the procedure must be taken.

An ultrasound scan is performed to confirm gestational age, viability of the foetus, liquor volume and placental site. The procedure takes about 15 minutes and is performed by a skilled operator. The procedure should be under continuous ultrasound control and be performed by a person doing at least 30 procedures a year. The sample is taken by needle aspiration under local anaesthetic using continuous ultrasound. The foetal heart is checked after the procedure and Anti-D given if appropriate.

In multiple pregnancies samples are taken from each sac and labelled with reference to placental site.

Some women may need haemostatic cover, such as DDAVP or recombinant coagulation factor concentrates, for the procedure depending on their diagnosis and level of coagulation factor.

Before leaving, arrangements should be made regarding the method of communication of the result.

Adverse events: The miscarriage rate is between 0.5-1%. An increased rate of miscarriage and fetal talipes has been associated with early amniocentesis (before 15 weeks). The woman is likely to experience minimal discomfort during the procedure.

Cord blood sampling

Fetal cord blood sampling to investigate haemostatic disorders is very rarely used in the UK and should only be considered if all other possible techniques can not be used or do not give conclusive results (Mibashan et al 1979). In the vast majority of cases molecular techniques will be available, will give more reliable results, have a lower risk of complications and a lower risk of artefact affecting the sample leading to misinterpretation of the results. Foetal cord sampling is a technique that should only be used to investigate severe deficiencies of coagulation factors where an undetectable level would suggest an affected foetus. In the majority of cases it should be possible to avoid foetal cord sampling by identifying the causative mutation in a carrier, even if an index case has not previously been studied, within a time frame that allows mutation analysis of the foetus using cells collected at amniocentesis or by CVS. Foetal cord sampling may be considered if a woman wishes to ensure that she does not have a child affected with severe haemophilia and a causative mutation can not be identified. Pre-test counselling should cover the possibility of artefactual, incorrect or uninterpretable results.

Procedure: In the investigation of X-linked disorders the foetal sex should be confirmed by molecular techniques using cells taken at amniocentesis. Ultrasound foetal sexing is not sufficiently reliable at this gestation to be used.

Foetal cord blood sampling should only be considered in tertiary referral fetal medicine units experienced in this technique. Written informed consent should be taken. A skilled operator can perform cord blood sampling from 18 weeks gestation. A blood sample is taken under continuous ultrasound control from either the umbilical vein at the placental insertion of the umbilical cord, foetal hepatic artery or foetal heart. There is a risk of the sample being contaminated by maternal blood leading to dilutional artefact or amniotic fluid diluting and activating the sample. One practice is to take three 1ml samples and test the first and third for coagulation factor levels to ensure these are consistent. The middle sample is tested for Hb and MCV and compared to the maternal MCV to confirm that the blood is of fetal origin.

Some women may need haemostatic cover, such as DDAVP or recombinant coagulation factor concentrates, for the procedure depending on their diagnosis and level of coagulation factor.

Adverse events: The procedure has a 1-2% risk of miscarriage in experienced departments.

Laboratory testing: A sample diluted by maternal blood may have an artefactually low level of all coagulation factors. A sample contaminated by amniotic fluid will be activated and there may have been consumption of all coagulation factors again resulting in an artefactually low level. The plasma should be tested for the coagulation factor under investigation and one other control coagulation factor level. Fibrinogen should be tested as a markedly reduced level would suggest activation of the sample and that other measured coagulation factor levels are unreliable. The results should be interpreted with regard to fetal blood normal ranges derived from the appropriate gestation. If two samples have been taken interpretation should only be undertaken if the results are consistent.

If the coagulation factor under investigation is undetectable and a control coagulation factor level, and fibrinogen level are within the expected range then a severe deficiency of that

coagulation factor is confirmed. The test results would normally be available within 24 hours. Samples from more than one foetus can be taken and labelled according to the placental site.

Preimplantation diagnosis

Preimplantation sexing and mutation analysis of embryos is technically feasible. Pre-implantation sexing with re-implantation of female embryos is currently being undertaken for haemophilia and is likely to become a realistic option for more couples over the next few years (Bui 2000 and Robertson 2003).

Studies for pre-implantation mutation analysis in haemophilia are currently being undertaken in a limited number of centres in the UK, who are licensed to perform the procedure by the HFEA. Each new test requires a new license.

Procedure: The ovaries are down regulated and then stimulated to produce multiple follicles. Ova are aspirated transvaginally, under ultrasound control. Heavy sedation is required. Ova are fertilized in vitro. Embryos at the 8 cell stage have one or two cells removed which are tested for either the sex or the known mutation. If available, up to two non-affected or female embryos are reimplanted. The main side effects are of ovarian hyperstimulation and multiple pregnancies. The success rate of in vitro fertilization is about 20-30%.

Detection of foetal cells from maternal blood

It is possible to detect foetal cells in the maternal circulation. Attention has focused on the fetal erythroblast as these cells have a short half-life in the maternal circulation and are abundant in early foetal blood. Currently the sensitivity and specificity of this testing is not sufficiently high for clinical practice. Studies are also being performed on cell-free foetal DNA in the maternal plasma. At present all of these techniques are at the research level.

Termination

If a woman decides to terminate her pregnancy management should be co-ordinated by an obstetric unit. The obstetric unit and the Haemophilia Centre should provide haemostatic cover, counselling and support as appropriate.

Suction termination of pregnancy under general anaesthetic can be performed up to 13-14 weeks gestation. After 13-14 weeks a medical termination is induced. It is important that the mother knows the gestation limit for suction termination for the obstetric unit in relation to the likely timing of results from antenatal diagnosis. For a termination after 21 weeks and 6 days foeticide using an intracardiac injection of KCl is mandatory to prevent the possibility of a live birth.

If selective termination of a dichorionic twin pregnancy is necessary the affected fetus is terminated using an intracardiac injection of concentrated KCl. This is not suitable for a monochorionic twin pregnancy, as both foetuses will be affected, and cord occlusion or laser techniques must be used. This procedure carries a 1% risk of miscarriage and some women opt to delay the selective termination until about 32 weeks when the unaffected foetus should survive, especially if the mother is given steroids to assist foetal lung maturity.

Acknowledgement: Mr B Beattie, University Hospital of Wales, Cardiff.

Section 6

Inherited bleeding disorders: the value of genetic testing in children

Scientific and technological advances have made it possible to establish the causative mutation in many families with haemophilia and other inherited bleeding disorders. This has significantly improved the quality of information that can be offered to families by allowing assessment of the risk of inhibitor formation in affected males, precise carrier detection and improved pre-natal diagnosis. However, it is recognised that genetic tests can only be performed on people who give informed consent after appropriate counselling and that some people decide that they would prefer not to know their genetic status for a variety of reasons.

Males with haemophilia

It is recommended that all children with haemophilia have their genotype established. This gives useful information regarding the risk of developing an inhibitor and may allow valuable information to be given to other family members. In the future individual genotype will be required if gene therapy becomes a realistic treatment option.

Females who are potential carriers

An area of particular difficulty revolves around testing female children who are potential carriers of haemophilia. This area is surrounded by potential ethical conflict and a distinction must be drawn between tests performed solely for future reproductive choice and those done to directly benefit the child in the immediate future. Under the 1989 Children's Act the child's views on testing should be sought and depending on the intellectual capacity of the child, a child younger than 16 years may give a valid consent providing the implications of the test are understood. Therefore, in order to be tested solely to inform future reproductive choices children must be in a position to understand the implications of the test and consent to it.

If children are tested before they are competent to give informed consent they are denied their right to refuse the test and the knowledge gained from that test. In addition, confidentiality is lost as it is possible that not all potential carriers of haemophilia would want their parents or other family members to know their status. The ability to gain future insurance may also be affected. It is therefore generally agreed that genetic tests should only be performed on children if the result leads to a direct benefit to the child or they are able to give informed consent. In haemophilia it is therefore inappropriate to offer to test females for carrier status before this knowledge is required to make reproductive choices.

The same reasoning holds true when performing antenatal diagnosis. The foetus should initially be sexed and if female it is accepted practice that no further tests should be performed unless the foetus is at risk of inherited haemophilia (eg Turner's syndrome).

However, in female children who are potential carriers of haemophilia it is important to establish whether they have an increased risk of bleeding to ensure appropriate treatment at times of surgery or trauma. It is therefore of benefit to these children to have their baseline coagulation factor levels tested. Coagulation factor levels in potential carriers of haemophilia should be measured after one year of age and when peripheral venous samples can be easily obtained. The tests should be performed earlier if required for a specific clinical reason. Tests should be performed on more than one occasion to ensure reproducible results.

Whilst knowledge of a low coagulation factor level is of direct clinical importance to a child it may also imply that she is a carrier of haemophilia. The potential benefit to the child in this circumstance is thought to outweigh the disadvantages and definitive carrier testing will still be required at a later date. Females with normal coagulation factor levels will not be at increased risk of bleeding but they may still be a carrier of haemophilia A or B. There is generally agreement that genetic testing to establish carrier status should be deferred in these cases until the child can give a valid consent for investigation.

To ensure that families understand the implications of the tests performed they should be sent written information of the result, its interpretation and an indication as to whether further genetic tests should be considered in the future. To avoid confusion all people tested should have their own individual case notes and record number.

The Genetics Working Party of the UKHCDO recommends the following guidelines on genetic testing in children:

- a) genetic tests can only be performed after written informed consent has been obtained.***
- b) boys with haemophilia should have their genotype established, as this has potential clinical benefit to the patient and his family.***
- c) phenotypic testing of females who are potential carrier should be performed when easy peripheral venepuncture is possible. Test should be performed when the children are more than one year of age (unless required earlier for a specific clinical reason) with results confirmed on at least two occasions.***
- d) genotypic testing for females who are potential carriers of haemophilia should be offered when the individual is able to understand the issues concerned and give informed consent.***
- e) in other inherited bleeding disorders all potentially affect children should be tested phenotypically.***
- f) individuals or families should be sent written information regarding the result and interpretation of any tests (genetic or phenotypic). This letter should indicate whether further genetic tests should be considered in the future.***
- g) all individuals tested should have their own set of case notes.***

Section 7

The Clinical - Laboratory Interface

Liaison and communication

For many Comprehensive Care Haemophilia Centres, the genetics laboratory forms part of the Centre. For some units, however, such services may be geographically separate and formal arrangements need to be in place to ensure appropriate and effective liaison and communication. A close relationship between the coagulation laboratory, the genetics laboratory and the clinical genetic counselling service is fundamental to the provision of a successful genetic diagnostic service. The laboratory-clinical interface is best maintained by regular meetings between the clinical and scientific staff to discuss genetics related issues including individual cases.

Within the comprehensive care centre regular meetings of clinical and laboratory staff from the genetics and coagulation laboratories are essential to review the genetics service, to identify any problems and to ensure the quality of the service.

Such meetings should include audit and review of the results of external quality assurance schemes. The results of recent laboratory studies should be reviewed. It is also important that meetings are held at regular intervals with Haemophilia Centres using the genetic diagnostic services of the comprehensive care centre in order to facilitate the appropriate provision of genetic services to patients and families attending all UK Haemophilia Centres.

A specification for a Haemophilia Genetics Laboratory is set out in [appendix IV](#).

Requests for Genetic Testing

There should be specific laboratory request forms for genetic studies in inherited bleeding disorders.

Clinical information: Sufficient information must be made available by the requesting clinician to enable the laboratory to investigate a family appropriately. A referral letter or request form identifying the disorder and its severity (clotting factor levels), the individuals requiring investigation and the investigations required, should be provided to the laboratory. The proband should be identified, and other relevant family details provided.

Pedigree: An accurate and appropriately detailed family tree is an essential prerequisite for genetic family studies. A copy of the family tree must always be provided to the laboratory by the clinical team along with the request for investigations. For further details refer to [Section 4](#).

Consent: Genetic testing can only be performed after written informed consent has been obtained. Receipt by the laboratory of a sample with a request for genetic diagnosis will be taken by the laboratory to indicate that appropriate informed consent has been obtained.

It is the responsibility of the clinician dealing with the particular case, and not the laboratory, to ensure that informed consent is obtained.

The laboratory should be made aware by the requesting clinician of any restriction on consent, eg storage of sample, and this should be indicated on the laboratory report. The completed consent form should be retained in the patient's notes and in the genetics file. Refer to [Section 4](#) with regard to confidentiality issues and disclosure of results.

Sample requirements and patient / sample identification: Details of samples required for laboratory services should be available to all staff members involved in genetic counselling. This information should also be available to outside hospitals / units / centres that may refer patients or samples for investigation. The clinician requesting the investigation should be clearly identified to the laboratory together with the address for reports. Known "high-risk of infection" samples should be appropriately identified, although the laboratory should consider all samples to be of high-risk and to be handled appropriately. The precise sample requirements and the type of anticoagulant may vary from centre-to-centre.

Samples and request forms must be clearly and accurately labelled with

- 1. the patient's first name and surname***
- 2. the patient's date of birth***

This is the minimum patient identification data set required for samples to be accepted for investigation.

Specimens must be clearly and reliably matched with the patient's details on the request form. The patient's hospital number or other unique identifier should also be provided. The use of a common hospital number for individuals within the same family is not acceptable. In the case of twins, some unique identifier (ie other than date of birth) must be supplied. A unique identifier will also be generated by the laboratory. The date of sample collection should be provided. Unlabelled samples will not be accepted by the laboratory. Samples from each patient or family member should be bagged separately with a separate request card for each individual sample. Each individual's post-code should be provided to the laboratory for workload monitoring / funding purposes.

Mutation Data

Up-to-date mutation data on individual patients and families must be made available by the laboratory to the clinical staff involved in patient management and genetic counselling.

All putative mutations must be assessed for likely pathogenic effect, and validated so far as possible in other affected family members. Their absence in non-affected family members should be confirmed where possible.

In some cases the family mutation may be known even though the patient may not have been investigated by that centre e.g. as part of studies performed elsewhere. Such data, if known, should be communicated to the laboratory on the request form together with a copy of the original report from the previous investigating laboratory. In cases where the family mutation has been identified elsewhere it is good practice for the current investigating laboratory to "confirm the mutation" using a new blood sample.

Laboratory Database

Accurate and readily accessible records of all stored samples and patient / family studies must be kept for all families with inherited bleeding disorders. Such records should include the results of genetic and phenotypic studies. Mutation information should be maintained on a controlled and confidential database, and appropriately transferred to the patient's notes.

Records must be updated regularly to reflect changes in relevant information that may become available, and effective liaison between clinicians, the genetics laboratory and the coagulation laboratory is a prerequisite. Regular meetings between laboratory and clinical staff to discuss the results of laboratory studies are considered to be essential. Liaison with other centres (see [Appendix V](#)) may be necessary to investigate rare disorders where such expertise does not exist within a specific centre.

In haemophilia A and B it is envisaged that the mutation will be sought in all families. For these reasons, regular updates of sample requirements from family members for outstanding mutation analysis should be made available. This is particularly important for mild cases of Haemophilia A or B, who may be seen infrequently.

Laboratory Reports

Laboratory reports should be timely, accurate and concise. The clinical question being asked should always be restated in the text. Reports should include the following:

- ***a brief summary section***
- ***the family pedigree including name and date of birth of each individual together with the determined genotype***
- ***an interpretative section***

Reports should be referenced so that the original mutational data can be readily accessed if necessary. When reporting gene-linkage analysis, the polymorphic markers used, haemophilia-associated alleles and other alleles identified should be clearly indicated. A key to any nomenclature used should be included. Any further tests required or information needed to allow further investigation should be detailed. Any factors unknown to the laboratory and which may, if present, affect interpretation of genetic data should be indicated (e.g. non-paternity, mosaicism). All reports should be signed and dated by the individual carrying out the laboratory tests, and appropriately authorised, for example by the scientific head of the laboratory.

A bullet point summary of the Clinical Molecular Genetics Society (CMGS) best practice guideline for report writing is provided in [Appendix VI](#). The full guideline is available on-line at www.cmgs.org.

Prenatal Diagnosis

Refer to [Section 5](#) for a full consideration. Close liaison between clinicians and scientific staff is essential for planning prenatal diagnosis. In addition to the laboratory performing the genetic diagnosis other individuals and departments need to be informed e.g. obstetrician, clinical geneticist, cytogenetics department. For X-linked disorders, clear protocols describing how to access foetal sexing services must be available. If a foetus is sexed as female then the

possibility of maternal contamination of the foetal sample must be excluded (eg by microsatellite DNA marker analysis).

A written protocol describing the local mechanisms of prenatal diagnosis should be provided to all of the clinical and laboratory services involved. A clear mechanism must be established to inform all relevant individuals of the results of antenatal diagnosis.

Where possible genetic testing to determine carrier status, and counselling regarding prenatal diagnosis, should be carried out before conception. This permits the laboratory to establish mutations or informative linkage markers in advance of any pregnancy and associated requests for prenatal diagnosis. This reduces the time and workload required for diagnosis, and allows more time to deal with any technical problems that may arise.

Research & Development

A close and effective laboratory-clinical interface is essential to facilitate research and development activities in the genetics of inherited bleeding disorders.

Mutation databases on the Internet

Details of reported mutations in inherited bleeding disorders, together with other important related information, are available at the following websites:

FVIII / haemophilia A:	http://europium.csc.mrc.ac.uk
FIX / haemophilia B:	http://www.kcl.ac.uk/ip/petergreen/haemBdatabase.html
VWF / VWD:	http://www.shef.ac.uk/vwf
FVII deficiency:	http://europium.csc.mrc.ac.uk
OMIM:	http://www3.ncbi.nlm.nih.gov/omim

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Appendix I

AGNC Revised Competency Draft

Communication skills

1. Establish a relationship with the client and elicit the client's concerns and expectations.
2. Elicit and interpret relevant medical, family and psychosocial history.
3. Convey clinical and genetic information to clients appropriate to their individual needs.
4. Explain the options available to the client, including risks, benefits and limitations.
5. Document information including case notes and correspondence in an appropriate manner.
6. Plan, organise and deliver professional and public education.

Interpersonal, counselling and psychosocial skills

7. Identify underlying concerns and respond to emerging issues of a client or family.
8. Acknowledge the implications of individual and family experiences, beliefs, values and culture for the genetic counselling process.
9. Make a psychosocial assessment of clients' needs and resources and provide support ensuring referral on to other agencies as appropriate.
10. Use a range of counselling skills to facilitate clients' adjustment and decision making.
11. Establish effective working relationships to function within a multidisciplinary genetics team and as part of the wider health and social care network.

Ethical Practice

12. Recognise and maintain professional boundaries.
13. Demonstrate reflective skills within the counselling context and in personal awareness for the safety of clients and families by participation in counselling/clinical supervision.
14. Act in accordance with AGNC Code of Ethical Conduct.
15. Present opportunities for clients to participate in research projects in a manner which facilitates informed choice.
16. Recognise his or her own limitations in knowledge and capabilities and seek consultation or refer clients when necessary.
17. Demonstrate continuing professional development as an individual practitioner and for the develop of the profession.

18. Contribute to the development and organisation of genetic services.

Critical thinking skills

19. Make appropriate genetic risk assessment.

20. Identify, organise, synthesize and summarise relevant medical and genetic information for use in genetic counselling.

21. Demonstrate the ability to organise and prioritise a caseload.

22. Identify and support clients' access to local, regional, and national resources and services.

23. Develop the necessary skills to critically analyse research findings to inform practice development.

Appendix II

Association Of Genetic Nurses And Counsellors (AGNC): Code Of Ethics

Introduction

This code of ethics¹ attempts to clarify and guide the conduct of genetic counsellors practising at both Levels One and Two of the Register of Genetic Counsellors. It acknowledges that ethical practice is essential in four main areas of responsibility, as listed below. All genetic counsellors must be aware of the ethical implications of their professional role, and adhere to the principles and guidelines in this code.

(A) Self-awareness and development

Genetic counsellors should:

- Recognise the limits of their own knowledge and abilities in any given situation, and decline any duties or responsibilities that cannot be carried out in a safe and competent manner
- Be responsible for their own physical and emotional health as it impacts on their professional performance
- Report to an appropriate person or authority any conscientious objection that may be relevant to their professional practice
- Maintain and improve their own professional education and competence

(B) Relationships with clients

Genetic counsellors should:

- Enable clients to make informed independent decisions, free from coercion
- Respect the client's personal beliefs and their right to make their own decisions
- Respect clients, irrespective of their ethnic origin, sexual orientation, religious beliefs and gender
- Avoid any abuse of their professional relationship with clients
- Protect all confidential information concerning clients obtained in the course of professional practice: disclosures of such information should only be made with the client's consent, unless disclosure can be justified because of a significant risk to others
- Report to an appropriate person or authority any circumstance, action or individual that may jeopardise client care, or their health and safety.
- Seek all relevant information required for any given client situation
- Refer clients to other competent professionals if they have needs outside the professional expertise of the genetic counsellor

(C) Relationships with colleagues

Genetic counsellors should:

- Collaborate and co-operate with other colleagues in order to provide the highest quality of service to the client
- Foster relationships with other members of the clinical genetics team, to ensure that clients benefit from a multidisciplinary approach to care
- Assist colleagues to develop their knowledge of clinical genetics and genetic counselling

- Report to an appropriate person or authority any circumstance or action which may jeopardise the health and safety of a colleague

Responsibilities within the wider society

Genetic counsellors should:

- Provide reliable and expert information to the general public
- Adhere to the laws and regulations of society. However, when such laws are in conflict with the principles of the profession, genetic counsellors should work toward change that will benefit the public interest
- Seek to influence policy makers on human genetic issues, both as an individual and through membership of professional bodies

Appendix III

HAEMOPHILIA CENTRE

INFORMATION ON GENETIC TESTING AND CONSENT FORM FOR PATIENTS AND FAMILIES WITH BLEEDING DISORDERS

Bleeding disorders may run in families and someone from your haemophilia centre will have explained to you how this affects your family. The purpose of this information sheet is to explain the reasons why you are being offered genetic tests and the consent form you will be asked to sign before these are performed.

Genetic tests may answer the following questions:

- Do you have the bleeding disorder?
- Are you a carrier of the bleeding disorder?
- If you are known to have a bleeding disorder, what is the genetic change that has caused your condition in your case?

Introduction

Why do we resemble our parents? How does a single cell grow into a whole human? Genetics is the science that tries to answer these questions. Humans, like every other living creature, are made up of cells. We all start off as one cell at the time of fertilisation. This cell contains two sets of genes, one from our mother and one from our father. For ease of storage and access, the genes are packaged up into 46 chromosomes. As the single cell divides the genes are copied so that every new cell possesses the full complement of genetic material. Genes are made of a chemical called DNA. Each cell holds an amazing two metres of DNA (deoxyribonucleic acid).

Humans have approximately 30,000 genes stretched out along their DNA. Each gene acts as the recipe for the production of a protein and together they make up the recipe book or blue print for you and me. Different genes or recipes are read at different times in different cells in response to the requirements of our bodies.

Sometimes genes, like recipes or blueprints, may have spelling mistakes in them or have bits missing. When this happens the proteins are either not produced or are abnormal. Genes, with these mistakes or mutations, function abnormally and so cause genetic disorders. Since genes are passed on from one generation to the next, genetic disorders often run in families. These mistakes can arise when a cell does not accurately copy its DNA. A mistake or variation in a single DNA letter can lead to disease.

Someone from your haemophilia centre has already explained the nature of the disorder and the manner in which it can be passed down through your family. If you require further information, or you are unclear about what you have been told, please ask for clarification or more help.

Genetic testing can tell us which people in your family have the condition and who are 'carriers' who might pass the disorder on to their own children. Simple tests of the defective clotting factor (coagulation factor) can sometimes tell us if a person is affected by the disorder or a carrier. Sometimes the level is normal even though a person is carrying a defective gene. With modern genetic techniques it is usually possible to locate the faulty genetic change in each family, although this can sometimes take time. Although many families may have the disorder, it is common for each family to have its own unique genetic change.

1. **What is the purpose of obtaining a blood sample?** It is very useful to know what the exact mistake in the DNA is that is causing the disorder in you/your child. Sometimes this helps us to be warned about how the disorder may respond to treatment in the future. Measurement of the blood coagulation factor level does not always clearly indicate if there is a genetic mistake present or not; analysis of the DNA is a more accurate way of telling this. For this a special type of blood sample is required from which the DNA can be extracted. A second sample may be taken from you on a separate occasion to confirm the result of the initial test.
2. **Where will the blood sample be tested?** The tests needed to detect a change ('spelling mistake' or bit missing) in DNA are specialised. Some of them are performed locally, but depending upon the nature of the disorder, it may be necessary to send your blood sample away to one of a small number of specialised laboratories. In all these, there are strict regulations in place to ensure complete confidentiality of your details.
3. **How long will the test take?** The answers to genetic tests often take some time to obtain. Your doctor will discuss the likely time course with you, as this varies with the disorder. It may take several months, or years if you have one of the less common, or more complicated disorders.
4. **How long will my blood sample be stored?** Sometimes it may not be possible with existing methods to find the genetic change in your family. In this case, the DNA will be stored until new tests are available. It is usual practice to store DNA samples indefinitely. Other new tests relevant to the disorder may arise in future, which will help us understand more about the mechanisms of the disorder.
5. **What are the risks of genetic testing?** In addition to information on the inheritance of a bleeding disorder, the results from these genetic tests are likely to be able to determine other information, such as confirmation of whether a child's parent is as assumed by the family. Therefore, occasionally unexpected results about family relationships arise from these tests, which, if known, could cause embarrassment within a family. If it is found, for example, that an individual's parent is different from that assumed by the family significant psychological problems can be caused and this may cause harm to the person being tested and other family members.

In some cases, identifying the faulty gene might affect individuals with regard to insurance and employment. Advice from an insurance or career advisor should be considered if necessary

The studies performed will be specific for the disorder known to be in your family. They will not exclude all forms of possible bleeding disorders.

6. **What else might be done with my blood sample?** We might want to use your sample to help develop or refine tests for bleeding disorders. In such cases your blood samples would not be linked back to you. The results would therefore be completely anonymous. From time to time it is very useful to run tests on a series of DNA samples anonymously to compare how common some changes in the DNA are which are not responsible for the condition. If your sample is used for such testing, no one will know whose it is, and there will be no comeback to you and your family.
7. **Who gets to know about the results?** The results will be told to you personally. Your family doctor will be sent the result.
8. **Why might it be useful for other members of my family to know about the results?** Information about the genetic disorder in you/your child is likely to be of benefit to other members of your family. It may, for example, be used to discover if a woman is a carrier and therefore if there is a risk of passing on the disorder to her children. With your permission we would like to be able to make the information about your genetic change available to doctors looking after other people in your family if they ask.
9. **Are my genetic results going to be stored anywhere other than in my hospital and GP case records?** There are local and national confidential databases, which keep information about genetic disorders of coagulation. We would like to record the information about your gene change. These databases are secure and protected.

If you would like to have your blood tested please read the consent form on the next page.

A) Patient Details

Surname Consultant

Forename Hospital Number

Date of Birth

B) Collection and usage of samples

I,.....(print name) give consent for a blood sample to be taken from(Myself or name of child) and the genetic material extracted, stored and tested for (specify disorder).

Please initial the boxes below to indicate your consent

- The purpose for obtaining this sample and the potential implications has been explained to me and have had an opportunity to have my questions answered.
- I have read and understood the above information about genetic testing.
- It is the intention to store the sample indefinitely.
- If no relevant test is currently available, I agree to the sample being stored until such time as an appropriate test is developed and the sample may then be tested.
- I understand that it may be necessary to use part of the sample anonymously for example for quality assurance or development of new tests. If any commercial benefits arise from studies no personal claim can be made.

Signed Date.....

(Patient/parent/legal guardian – delete as appropriate)

C) Use and availability of results

- I hereby give consent for clinical and genetic information that may be relevant to other family members to be made available to relevant health care professionals.
- I agree to the results being entered into local confidential databases.
- I agree to the results being entered into national confidential databases

Signed Date.....

(Patient/parent/legal guardian – delete as appropriate)

D) Person obtaining consent

I have explained to the above patient/parent/legal guardian the purpose of obtaining a sample for genetic studies and their implications.

Signed Date.....

Print Name Position.....

Appendix IV

The Haemophilia Genetics Laboratory and availability of Genetic Diagnostic Services in the UK: Specification for Haemophilia Genetics Laboratory

The Network functions to ensure the provision nationally of a robust and high-quality genetic diagnostic service for the inherited bleeding disorders. A directory of laboratories affiliated to the Network, identifying services available and contact details, is reproduced within this document. The Directory is also available from all haemophilia centres and from the UKHCDO Secretariat (e-mail: lynne.dewhurst@cmmc.nhs.uk).

UK laboratories providing a genetic diagnostic service for haemophilia and other inherited bleeding disorders should be affiliated to the UKHCDO Haemophilia Genetics Laboratory Network.

UKHCDO Haemophilia Genetics Laboratory Network-affiliated laboratories are required to comply with the following quality standards:

1. NHS provided and funded molecular genetics laboratory within the Comprehensive Care Haemophilia Centre
2. Facilities and expertise to allow the identification of mutations in haemophilia A and B (including handling risk of infection samples)
3. Ability to assign carriership and make antenatal diagnosis
4. Turnaround time to reporting of six weeks for the majority of samples and two weeks for urgent ones, eg to allow antenatal diagnosis in newly presenting pregnant females
5. CPA accreditation
6. Participation in appropriate genetics external quality control scheme (currently NEQAS)
7. Active collaboration between all haemophilia genetic laboratories to provide a robust service available throughout the year

Assessment of compliance with these standards is an integral part of the external peer-review audit system operated by the UKHCDO for UK haemophilia centres.

Adequate numbers of appropriately qualified state-registered staff are required to provide a high-quality and up-to-date genetic diagnostic service in accordance with the quality standards identified above. Professional direction for the laboratory should be provided by a medically qualified consultant haematologist / geneticist or a state-registered consultant clinical scientist.

Appendix V

Directory of Molecular Diagnostic Services for Inherited Bleeding Disorders

Haemophilia A

<i>Centre</i>	<i>Description of Service</i>	<i>Contact details</i>
Belfast	FVIII gene intron 22 inversion (long PCR) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (CSGE & sequencing) Gene linkage analysis Carrier and prenatal diagnosis	Dr Paul Winter Principal Clinical Scientist Department of Haematology C Floor Belfast City Hospital Lisburn Road Belfast B19 7AB Tel: 028 9032 9241 ext 3225 / 3097 Fax: 028 9026 3527 e-mail: paul.winter@bll.n-i.nhs.uk
Birmingham	FVIII gene intron 22 inversion (long PCR) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (CSGE & sequencing) Gene linkage analysis Carrier and prenatal diagnosis	Dr Said Enayat Principal Clinical Scientist Dr Bim Theophilus Senior Clinical Scientist Molecular Haemostasis Laboratory Department of Haematology Birmingham Children's Hospital NHS Trust Steelhouse Lane Birmingham B4 6NH Tel: 0121 333 9861 Fax: 0121 333 9841 e-mail: said.enayat@bhamchildrens.wmids.nhs.uk bimal.theophilus@bhamchildrens.wmids.nhs.uk
Cardiff	FVIII gene intron 22 inversion (long PCR) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Gene linkage analysis Carrier and prenatal diagnosis	Dr Derrick Bowen Senior Lecturer Department of Haematology University of Wales College of Medicine Heath Park Cardiff CF14 4XN Tel: 029 2074 2154 Fax: 029 2074 4655 e-mail: bowendjl@cardiff.ac.uk

Haemophilia A

<p>Edinburgh</p>	<p>FVIII gene intron 22 inversion (long PCR) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (PCR & direct sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Dr David Stirling Consultant Clinical Scientist</p> <p>Department of Haematology Royal Infirmary of Edinburgh Edinburgh EH3 9YW</p> <p>Tel: 0131 536 2142 Fax: 0131 536 2145 e-mail: david.stirling@ed.ac.uk</p>
<p>London (Guy's & St Thomas' NHS Trust)</p>	<p>FVIII gene intron 22 inversion (long PCR) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (dHPLC & sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Mr Mike Mitchell Principal Clinical Scientist Ms Jacky Cutler Chief Biomedical Scientist</p> <p>Molecular Genetics Haemophilia Reference Centre Guy's & St Thomas' NHS Trust St. Thomas' Hospital, London SE1 7EH.</p> <p>Tel: 0207 928 9292 ext 3739 or 0207 922 8267 Fax: 0207 620 1659 or 0207 401 3125 e-mail: mike.mitchell@gstt.sthames.nhs.uk Jacqueline.cutler@gstt.sthames.nhs.uk</p>
<p>London (Royal Free Hospital)</p>	<p>FVIII gene intron 22 inversion (Southern blot) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (PCR & direct sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Ms G Mellars Chief BMS</p> <p>Molecular Diagnostic Laboratory Haemophilia & Haemostasis Unit Royal Free Hospital Pond Street London NW3 2QG</p> <p>Tel: 0207 472 6412 Fax: 0207 830 2879 e-mail: g.mellars@rfc.ucl.ac.uk</p>

Haemophilia A

<p>Manchester</p>	<p>FVIII gene intron 22 inversion (long PCR) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (PCR & direct sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Dr Tony Cumming Consultant Clinical Scientist Dr Steve Keeney Principal Clinical Scientist</p> <p>Molecular Diagnostics Centre Top-floor Multi-Purpose Building Manchester Royal Infirmary Oxford Road Manchester M13 9WL</p> <p>Tel: 0161 276 4880 (TC) / 5990 (SK) / 4809 (lab) Fax: 0161 276 5989 e-mail: tcumming@labmed.cmht.nwest.nhs.uk skeeney@labmed.cmht.nwest.nhs.uk</p>
<p>Newcastle</p>	<p>FVIII gene intron 22 inversion (Southern blot) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (dHPLC & sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Dr Su Stenhouse Dr Ann Curtis</p> <p>Northern Genetics Service Institute of Human Genetics International Centre for Life Central Parkway Newcastle-upon Tyne NE1 3BZ</p> <p>Tel: 0191 241 7885 (SS) / 8772 (AC) Fax: 0191 241 8799 e-mail: s.a.r.stenhouse@ncl.ac.uk ann.curtis@ncl.ac.uk</p>
<p>Nottingham</p>	<p>FVIII gene intron 22 inversion (long PCR) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (CSGE & sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Dr Marian Hill Senior Clinical Scientist Mrs Sue Kalsheker Senior Clinical Scientist</p> <p>Molecular Diagnostics Department of Clinical Chemistry University Hospital Queen's Medical Centre Nottingham NG2 7UH</p> <p>Tel: 0115 875 4593 Fax: 0115 970 9189 e-mail: marian.hill@nottingham.ac.uk susan.kalsheker@nottingham.ac.uk</p>

Haemophilia A

Sheffield	FVIII gene intron 22 inversion (long PCR) FVIII gene intron 1 inversion (PCR) Detection of known FVIII gene mutation (PCR & sequencing) Full FVIII gene mutation screening (CSGE & sequencing) Gene linkage analysis Carrier and prenatal diagnosis	Dr Anne Goodeve Honorary Clinical Scientist & Reader in Molecular Medicine Mandy Nesbitt Clinical Scientist Molecular Haematology Department G-floor Royal Hallamshire Hospital Sheffield S10 2JF Tel: 0114 271 3339 Fax: 0114 271 3201 e-mail: a.goodeve@sheffield.ac.uk
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Haemophilia B

<i>Centre</i>	<i>Description of Service</i>	<i>Contact details</i>
Belfast	Detection of known FIX gene mutation (PCR & sequencing) Gene linkage analysis Carrier and prenatal diagnosis	Dr Paul Winter Principal Clinical Scientist Department of Haematology C Floor Belfast City Hospital Lisburn Road Belfast B19 7AB Tel: 028 9032 9241 ext 3225 / 3097 Fax: 028 9026 3527 e-mail: paul.winter@bll.n-i.nhs.uk
Birmingham	Detection of known FIX gene mutation (PCR & sequencing) Full FIX gene mutation screening (CSGE & sequencing) Carrier and prenatal diagnosis	Dr Said Enayat Principal Clinical Scientist Dr Bim Theophilus Senior Clinical Scientist Molecular Haemostasis Laboratory Department of Haematology Birmingham Children's Hospital NHS Trust Steelhouse Lane Birmingham B4 6NH Tel: 0121 333 9861 Fax: 0121 333 9841 e-mail: said.enayat@bhamchildrens.wmids.nhs.uk bimal.theophilus@bhamchildrens.wmids.nhs.uk
Cardiff	Detection of known FIX gene mutation (PCR & sequencing) Full FIX gene mutation screening (PCR & direct sequencing) Gene linkage analysis Carrier and prenatal diagnosis	Dr Derrick Bowen Senior Lecturer Department of Haematology University of Wales College of Medicine Heath Park Cardiff CF14 4XN Tel: 029 2074 2154 Fax: 029 2074 4655 e-mail: bowendj1@cardiff.ac.uk

Haemophilia B

<p>Edinburgh</p>	<p>Detection of known FIX gene mutation (PCR & sequencing) Full FIX gene mutation screening (PCR & direct sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Dr David Stirling Consultant Clinical Scientist</p> <p>Department of Haematology Royal Infirmary of Edinburgh Edinburgh EH3 9YW</p> <p>Tel: 0131 536 2142 Fax: 0131 536 2145 e-mail: david.stirling@ed.ac.uk</p>
<p>London (Guy's & St Thomas' NHS Trust)</p>	<p>Detection of known FIX gene mutation (PCR & sequencing) Full FIX gene mutation screening (dHPLC & sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Mr Mike Mitchell Principal Clinical Scientist Ms Jacky Cutler Chief Biomedical Scientist</p> <p>Molecular Genetics Haemophilia Reference Centre Guy's & St Thomas' NHS Trust St. Thomas' Hospital, London SE1 7EH.</p> <p>Tel: 0207 928 9292 ext 3739 or 0207 922 8267 Fax: 0207 620 1659 or 0207 401 3125 e-mail: mike.mitchell@gstt.sthames.nhs.uk Jacqueline.cutler@gstt.sthames.nhs.uk</p>
<p>London (Royal Free Hospital)</p>	<p>Detection of known FIX gene mutation (PCR & sequencing) Full FIX gene mutation screening (PCR & direct sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Ms G Mellars Chief BMS</p> <p>Molecular Diagnostic Laboratory Haemophilia & Haemostasis Unit Royal Free Hospital Pond Street London NW3 2QG</p> <p>Tel: 0207 472 6412 Fax: 0207 830 2879 e-mail: g.mellars@rfc.ucl.ac.uk</p>

Haemophilia B

<p>Manchester</p>	<p>Detection of known FIX gene mutation (PCR & sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Dr Tony Cumming Consultant Clinical Scientist Dr Steve Keeney Principal Clinical Scientist</p> <p>Molecular Diagnostics Centre Top-floor Multi-Purpose Building Manchester Royal Infirmary Oxford Road Manchester M13 9WL</p> <p>Tel: 0161 276 4880 (TC) / 5990 (SK) / 4809 (lab) Fax:: 0161 276 5989 e-mail: tcumming@labmed.cmht.nwest.nhs.uk skeeney@labmed.cmht.nwest.nhs.uk</p>
<p>Nottingham</p>	<p>Detection of known FIX gene mutation (PCR & sequencing) Full FIX gene mutation screening (CSGE & sequencing) Carrier and prenatal diagnosis</p>	<p>Dr Marian Hill Senior Clinical Scientist Mrs Sue Kalsheker Senior Clinical Scientist</p> <p>Molecular Diagnostics Department of Clinical Chemistry University Hospital Queen's Medical Centre Nottingham NG2 7UH</p> <p>Tel: 0115 875 4593 Fax: 0115 970 9189 e-mail: marian.hill@nottingham.ac.uk susan.kalsheker@nottingham.ac.uk</p>
<p>Sheffield</p>	<p>Detection of known FIX gene mutation (PCR & sequencing) Full FIX gene mutation screening (CSGE & sequencing) Gene linkage analysis Carrier and prenatal diagnosis</p>	<p>Dr Anne Goodeve Honorary Clinical Scientist & Reader in Molecular Medicine Mandy Nesbitt Clinical Scientist</p> <p>Molecular Haematology Department G-floor Royal Hallamshire Hospital Sheffield S10 2JF</p> <p>Tel: 0114 271 3339 Fax: 0114 271 3201 e-mail: a.goodeve@sheffield.ac.uk</p>

von Willebrand Disease

<i>Centre</i>	<i>Description of Service</i>	<i>Contact details</i>
Belfast	Genetic analysis of VWF gene exon 28 in types 2A, 2B and 2M VWD	<p>Dr Paul Winter Principal Clinical Scientist</p> <p>Department of Haematology C Floor Belfast City Hospital Lisburn Road Belfast B19 7AB</p> <p>Tel: 028 9032 9241 ext 3225 / 3097 Fax: 028 9026 3527 e-mail: paul.winter@bll.n-i.nhs.uk</p>
Birmingham	<p>Type 1 and 3 VWD: Gene linkage analysis of common polymorphisms and intron 40 VNTRs Full VWF gene mutation screening by CSGE & sequencing</p> <p>Type 2A, 2B, 2M & 2N VWD: VWF gene mutation screening by CSGE & sequencing</p>	<p>Dr Said Enayat Principal Clinical Scientist Dr Bim Theophilus Senior Clinical Scientist</p> <p>Molecular Haemostasis Laboratory Department of Haematology Birmingham Children's Hospital NHS Trust Steelhouse Lane Birmingham B4 6NH</p> <p>Tel: 0121 333 861 Fax: 0121 333 9841 e-mail: said.enayat@bhamchildrens.wmids.nhs.uk bimal.theophilus@bhamchildrens.wmids.nhs.uk</p>
Cardiff	<p>Detection of known VWF gene mutation (PCR & sequencing) Targeted screen for common type 2A, 2B and 2N mutations (PCR & heteroduplex analysis) Linkage analysis (SNPs and VNTRs)</p>	<p>Dr Derrick Bowen Senior Lecturer</p> <p>Department of Haematology University of Wales College of Medicine Heath Park Cardiff CF14 4XN</p> <p>Tel: 029 2074 2154 Fax: 029 2074 4655 e-mail: bowendjl@cardiff.ac.uk</p>

von Willebrand Disease

<p>Edinburgh</p>	<p>Detection of known VWF mutation (PCR & sequencing) Targeted and full VWF gene mutation screening (PCR & direct sequencing)</p>	<p>Dr David Stirling Consultant Clinical Scientist</p> <p>Department of Haematology Royal Infirmary of Edinburgh Edinburgh EH3 9YW</p> <p>Tel: 0131 536 2142 Fax: 0131 536 2145 e-mail: david.stirling@ed.ac.uk</p>
<p>London (Guy's & St Thomas' NHS Trust)</p>	<p>Detection of known VWF gene mutation (PCR & sequencing) Targeted and full VWF gene mutation screening (dHPLC & direct sequencing) Gene linkage analysis (intron 40 VNTRs)</p>	<p>Mr Mike Mitchell Principal Clinical Scientist Ms Jacky Cutler Chief Biomedical Scientist</p> <p>Molecular Genetics Haemophilia Reference Centre Guy's & St Thomas' NHS Trust St. Thomas' Hospital, London SE1 7EH.</p> <p>Tel: 0207 928 9292 ext 3739 or 0207 922 8267 Fax: 0207 620 1659 or 0207 401 3125 e-mail: mike.mitchell@gstt.sthames.nhs.uk Jacqueline.cutler@gstt.sthames.nhs.uk</p>
<p>London (Royal Free Hospital)</p>	<p>Screening for VWF gene mutations in types 2A, 2B,2M and 2N VWD</p>	<p>Ms G Mellars Chief BMS</p> <p>Molecular Diagnostic Laboratory Haemophilia & Haemostasis Unit Royal Free Hospital Pond Street London NW3 2QG</p> <p>Tel: 0207 472 6412 Fax: 0207 830 2879 e-mail: g.mellars@rfc.ucl.ac.uk</p>

von Willebrand Disease

<p>Manchester</p>	<p>Detection of known VWF gene mutation (PCR & sequencing) Targeted and full VWF gene mutation screening (PCR & direct sequencing) Gene linkage analysis (intron 40 VNTRs)</p>	<p>Dr Tony Cumming Consultant Clinical Scientist Dr Steve Keeney Principal Clinical Scientist</p> <p>Molecular Diagnostics Centre Top-floor Multi-Purpose Building Manchester Royal Infirmary Oxford Road Manchester M13 9WL</p> <p>Tel: 0161 276 4880 (TC) / 5990 (SK) / 4809 (lab) Fax: 0161 276 5989 e-mail: tcumming@labmed.cmht.nwest.nhs.uk skeeney@labmed.cmht.nwest.nhs.uk</p>
<p>Nottingham</p>	<p>Mutation screening in type 2N VWD Genetic analysis of VWF gene exon 28 in types 2A, 2B, and 2M VWD</p>	<p>Dr Marian Hill Senior Clinical Scientist Mrs Sue Kalsheker Senior Clinical Scientist</p> <p>Molecular Diagnostics Department of Clinical Chemistry University Hospital Queen's Medical Centre Nottingham NG2 7UH</p> <p>Tel: 0115 875 4593 Fax: 0115 970 9189 e-mail: marian.hill@nottingham.ac.uk susan.kalsheker@nottingham.ac.uk</p>
<p>Sheffield</p>	<p>Genetic analysis of VWF gene exon 28 for types 2A, 2B and 2M VWD Detection of known VWF gene mutation (PCR & sequencing) Full VWF gene mutation screening (PCR & direct sequencing) Gene linkage analysis (intron 40 STRs)</p>	<p>Dr Anne Goodeve Honorary Clinical Scientist & Reader in Molecular Medicine Mandy Nesbitt Clinical Scientist</p> <p>Molecular Haematology Department G-floor Royal Hallamshire Hospital Sheffield S10 2JF</p> <p>Tel: 0114 271 3339 Fax: 0114 271 3201 e-mail: a.goodeve@sheffield.ac.uk</p>

Other inherited bleeding disorders

Fibrinogen

<i>Centre</i>		<i>Contact details</i>
Belfast	Department of Haematology C Floor Belfast City Hospital Lisburn Road Belfast B19 7AB	Dr Paul Winter Principal Clinical Scientist Tel: 028 9032 9241 ext 3225 / 3097 Fax: 028 9026 3527 e-mail: paul.winter@bll.n-i.nhs.uk
Edinburgh	Department of Haematology Royal Infirmary of Edinburgh Edinburgh EH3 9YW	Dr David Stirling Consultant Clinical Scientist Tel: 0131 536 2142 Fax: 0131 536 2145 e-mail: david.stirling@ed.ac.uk
London	Molecular Genetics Haemophilia Reference Centre Guy's & St Thomas' NHS Trust St. Thomas' Hospital London SE1 7EH	Mr Mike Mitchell Principal Clinical Scientist Ms Jacky Cutler Chief Biomedical Scientist Telephone: 0207 928 9292 ext 3739 or 0207 4013125 Fax: 0207 620 1659 or 0207 401 3125 e-mail: mike.mitchell@gstt.sthames.nhs.uk
Nottingham	Molecular Diagnostics Department of Haematology and Clinical Chemistry University Hospital Queen's Medical Centre Nottingham NG2 7UH	Dr Marian Hill Senior Clinical Scientist Mrs Sue Kalsheker Senior Clinical Scientist Tel: 0115 875 4593 Fax: 0115 970 9189 e-mail: marian.hill@nottingham.ac.uk susan.kalsheker@nottingham.ac.uk

Prothrombin

- No labs report diagnostic service

Factor V

<i>Centre</i>		<i>Contact details</i>
London	Molecular Genetics Haemophilia Reference Centre Guy's & St Thomas' NHS Trust St.Thomas' Hospital, London SE1 7EH.	Mr Mike Mitchell Principal Clinical Scientist Ms Jacky Cutler Chief Biomedical Scientist Tel: 0207 928 9292 ext 3739 or 0207 922 8267 Fax: 0207 620 1659 or 0207 401 3125 e-mail: mike.mitchell@gstt.sthames.nhs.uk Jacqueline.cutler@gstt.sthames.nhs.uk

Factor VII

<i>Centre</i>		<i>Contact details</i>
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Platelet Disorders - Bernard Soulier

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Platelet Disorders – Glanzmann's

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Appendix VI

Clinical Molecular Genetics Society (CMGS) best practice guideline for report writing

The full guideline is available on-line at www.cmgs.org/.

- Reports must be clear, concise, accurate, fully interpretive, credible and authoritative.
- Patients must be identified by at least two items of information – most often the full name + date of birth and hospital number. Use of laboratory number and pedigree / family number is recommended, particularly when several reports are written on different family members.
- Reports should explicitly restate the clinical question being asked, including:
 - the disease being investigated
 - the request being made (eg carrier diagnosis)
 - the indication (eg known family history)
- Include brief details of the tests used in the analysis, including sensitivity estimates if appropriate.
- Present laboratory results in a brief unambiguous form. The use of a table is particularly recommended to present the results of linkage analysis studies.
- Reports should include a pedigree diagram, with sufficient information to unambiguously identify the family (include unique family / pedigree number) and to distinguish each relevant person.
- Pedigree diagrams should include only those individuals relevant to the interpretation – the confidentiality of relatives of the patient being reported must be a consideration. It is recommended to restrict the number of individuals reported to those essential for accurate analysis.
- A key should be included to any nomenclature used. The use of “+” and “-“ can be open to misinterpretation and is best avoided.
- It is important to provide a full interpretation of the molecular genetic test results, considered in the context of relevant clinical and family information supplied at referral.
- When appropriate, genetic carrier risks should be stated.
- Include a statement of the interpretation of the genotyping results. It is useful to highlight this statement.
- Where appropriate refer to the possibility of errors which may arise due to factors beyond the control of the laboratory (eg risk of non-paternity).

It may be useful to give references where recently published data have a bearing on interpretation or risk calculation.