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Genetic Testing for Hereditary Pancreatitis: Guidelines for Indications, Counselling, Consent and Privacy Issues

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for the Consensus Committees of the European Registry of Hereditary Pancreatic Diseases, the Midwest Multi-Center Pancreatic Study Group and the International Association of Pancreatology

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Background

The identification of point mutations in the cationic trypsinogen (PRSS1) gene that underlie hereditary pancreatitis (HP) has added a valuable diagnostic test to the investigation of acute and chronic pancreatitis. A small blood sample will allow a comparatively cheap test to be performed by paediatricians, gastroenterologists and pancreatic surgeons. Testing DNA for such a high-risk, high-penetrance gene is non-invasive when compared to current investigations, e.g. ERCP or pancreatic function testing. However, the possible adverse effects of unrestrained molecular genetic testing must be emphasized. Mutation testing for the commoner R122H and N29I (and A16V) mutations in the cationic trypsinogen (serine protease, PRSS1) gene (OMIM No. 276000) has previously been performed under the regulation of Ethics Committee Approved Research Protocols. It is now frequently requested in routine clinical practice and as a consequence is becoming more widely available via health service-funded or commercial molecular genetics testing laboratories outside the research setting. In this document, we refer to PRSS1 mutation testing for HP, as this is currently accepted as a clinically useful genetic test, outside the context of a research study. Research programmes are looking at other genes that may be involved in the development of pancreatitis, e.g. PSTI/SPINK1 [Witt et al., 2000; Pfützer et al., 2000], and the role of mutations in the cystic fibrosis (CFTR) gene [Sharer et al., 1998; Cohn et al., 1998] in determining chronic pancreatitis. More gene(s) and their mutation(s) will be defined for HP, and ultimately for familial pancreatic cancer as research proceeds. We would expect these consensus guidelines to apply to new tests as they are developed and recognized to be clinically useful in the service setting. At present, we only regard PRSS1 mutation testing as of clinical service benefit. All other molecular genetic tests for pancreatitis should currently (July, 2001) be performed on a research basis with an appropriate Research Ethics Committee Approved Protocol.

This paper summarizes the current situation and suggests proper ethical principles upon which we believe service-based genetic testing should proceed. We propose consensus guidelines for ethical molecular genetic testing

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for HP. A joint United States-United Kingdom publication [Applebaum et al., 2000] from the Midwest Multicenter Pancreatic Study Group and the European Registry of Hereditary Pancreatic Diseases (EUROPAC) Study Group described 'Counselling, Laboratory And Regulatory Issues for Ethical Research in Multi-Centre Studies of Inherited Pancreatic Diseases'. We take these as a starting point for what has become a point of transition, as molecular genetic testing for HP becomes more widely available and is being introduced into routine clinical practice. We hope to ensure the same high ethical standards and best practice by a wider range of requesting clinicians. Our guidelines are built upon the desire to maximize patient autonomy in decision making, ensuring fully informed consent and respect for individual choice and non-directive and non-judgmental genetic counselling.

The Decision to Offer Diagnostic Molecular Genetic Testing

We are aware that with the introduction of any new test there is a desire to 'try it out'. We set out specific indications for the decision to offer diagnostic molecular genetic testing for HP. Outside of defined Ethics Committee Approved Research Protocols, the indication for PRSS1 mutation analysis in a symptomatic patient should be any of the following: (1) recurrent (2 or more separate, documented episodes with hyper-amylasaemia) attacks of *acute* pancreatitis for which there is no explanation (anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidaemia, etc.), or (2) unexplained (idiopathic) *chronic* pancreatitis, or (3) a family history of pancreatitis in a first-degree (parent, sib, child) or second-degree (aunt, uncle, grandparent) relative, or (4) an unexplained episode of documented pancreatitis occurring in a child that has required hospitalization, and where there is significant concern that HP should be excluded (see 'The Genetic Testing of Children' below), or (5) patients with pancreatitis eligible for an Ethics Committee Approved Research Protocol.

The above criteria focus on patients who have already manifested pancreatitis that has raised the clinical suspicion of HP. We are aware that the incomplete penetrance, variability of expression and the description of a new mutation of PRSS1 may obscure a positive family history. Clearly, there must be clinical freedom to arrange PRSS1 molecular genetic testing in 'grey' areas whilst guarding against a *screen-all* approach.

Pre-Test HP Information prior to Diagnostic PRSS1 Molecular Genetic Testing

The detail into which any referring clinician goes with the following points will vary from setting to setting. It cannot easily be prescribed, but a pre-test information sheet (as can be downloaded from www.liv.ac.uk/surgery/europac.html, www.mmpsg.org and www.pancreas.org in English and from www.pancreas.de in German) given to the patient after a clinic discussion is one approach. We believe that formal specialist genetic counselling is not required before the diagnostic genetic testing of a symptomatic adult, provided the nine prerequisite points listed below have been covered. We now support the offer of molecular genetic testing for HP by paediatricians, gastroenterologists and pancreatic surgeons in routine clinical practice, and outside of research studies. By opening what has been previously termed a 'pancreatic Pandora's box', we trust that other clinicians will use the test with care, after adequate patient preparation. We suggest that informed consent is documented before the test and that detailed pre-test information be given (consent forms are available from www.europac.liv.ac.uk, www.mmpsg.org and www.pancreas.org in English and from www.pancreas.de in German). Outside the context of a research study, as a minimum, the following points should be covered in a service testing setting:

(1) Why the test has been suggested and obtaining documented informed consent.

(2) The implications of finding an HP-related mutation in the PRSS1 gene for the health and medical care of that patient.

(3) How the genetic test result will be communicated to the patient, and who else will be informed of their result.

(4) The availability of genetic counselling after the test result is known.

(5) Apart from informing the patient, it would be usual practice for that laboratory result to also go to the clinician who has requested that test, other involved pancreatic specialists and the family doctor if appropriate.

(6) The pancreatic cancer risk and the possible adverse health and life insurance and employment consequences for the patient (if not safeguarded against by national legislation).

(7) The implications of a positive genetic test result for the patient's relatives.

(8) Testing of the sample in an approved health service-funded or commercial molecular genetics testing laboratory with appropriate quality control standards.

(9) Finding out whether the patient's test sample may then be used for any research project, and by what (anonymous) route this will occur.

Genetic Information following a Positive HP Molecular Genetic Test Result

Providing a patient has been adequately prepared before their HP molecular genetic test, they should not be surprised by a positive test result, or by the implications when they are then explained to him/her. Should an HP mutation be found, good-quality genetic counselling from a recognized specialist genetic counselling service must then be offered in order to discuss the following points in more detail:

(1) What the test result is, in terms of which gene mutation has been found, preferably in written form.

(2) A description of the (autosomal) mode of inheritance and incomplete penetrance, and an emphasis on the variability of expression in lay terms that are easily understood by the patient and their family.

(3) That the disease course and severity cannot be easily predicted, but that chronic pancreatitis, pancreatic exocrine and endocrine insufficiency are likely complications.

(4) That the lifetime pancreatic cancer risk is estimated to be approximately 40% [Lowenfels et al., 1993, 1997; Howes et al., 2000].

(5) What current management exists for pancreatic follow-up and pancreatic cancer risk surveillance.

(6) The risks for relatives of inheriting this HP gene mutation, and their risks of developing pancreatitis.

(7) A plan for the patient to inform their family of their test result, and the options for pancreatic investigation, genetic counselling and if appropriate, genetic testing.

(8) The patient should be encouraged, but not coerced, into telling their at-risk relatives.

(9) What further research is available in this and related areas that the patient might be interested in joining.

These points focus on the genetic aspects of a test result. Clearly, the discussion will also cover many general pancreatic and surgical issues. Ideally, the patient should be seen in a multi-disciplinary clinic that can address many of these issues with a clear, coherent and consistent management plan.

Predictive Genetic Testing for HP

The predictive (pre-symptomatic) testing of unaffected relatives raises complex and competing issues. This is referred to specifically here and in detail. There is the desire to reassure unaffected relatives that they are indeed not gene carriers and not liable to develop HP or to pass it on. However, gene carriers who are young are still liable to present with their first episode of acute pancreatitis. This raises the question of testing children and the issue of protecting their autonomy until they reach an age when they can give fully informed consent for themselves. Would a 10 year old found to be an HP mutation carrier thank their parents if they later encounter difficulties with life or health insurance or in gaining employment when they actually remain symptom free? The balance shifts in favour of predictive testing if insurance issues can be safeguarded against, as has been done by the legislature in Germany. If effective interventions for HP mutation carriers are developed that protect against episodes of acute pancreatitis or the development of chronic pancreatitis or pancreatic cancer, then the balance will also swing more towards advocating predictive testing.

In the meantime, it is essential that careful and specialized genetic counselling is offered to all unaffected adults who are contemplating predictive genetic testing for HP. This group is especially vulnerable to the unwelcome and unexpected consequences of molecular genetic testing for HP. Service-based predictive testing is only suitable for the first-degree relatives of an HP patient who carries an already defined HP gene (PRSS1) mutation that has an accepted clinical phenotype. Predictive genetic testing should only be offered by a recognized service with adequate pre-test counselling, post-test support and clinical follow-up. The steps involved should include the following:

(1) The person must have a first-degree relative with a defined HP gene mutation.

(2) The person should be over 16 years of age and able to make an independent and fully informed decision. Although in some countries a parental request for genetic testing of an underage child cannot legally be declined, the above issues should be discussed with the parents in detail and the child's preferences should be taken into account.

(3) Ideally, there should be a consistently stated (over at least 3 months since first contact) request for predictive testing.

(4) The person should understand the (autosomal dominant) mode of inheritance and the incomplete penetrance of HP mutations.

(5) There should have been discussion with the person on the possible implications of finding they are an HP mutation carrier on their own health and whether this will lead to increased anxiety and possible stigmatization, for example.

(6) It should be emphasized that if they are found to be an HP mutation carrier they cannot predict their own disease severity by comparison with their affected relatives.

(7) The person should be informed that they are likely (80% gene penetrance) to have attacks of acute pancreatitis [Whitcomb et al., 1996]. Current evidence indicates that if a person remains symptom free until the age of 20, there is about a 25% residual risk, and by the age of 30 years, a 10% residual risk of still manifesting HP and its attendant complications [Ellis et al., 2000].

(8) The person should be informed that if they manifest attacks of pancreatitis, they are likely to go on to develop chronic pancreatitis and possibly pancreatic exocrine and endocrine insufficiency and will have a lifetime risk of pancreatic cancer estimated at over 40% [Lowenfels et al., 1993, 1997; Howes et al., 2000].

(9) The current management for pancreatic follow-up and pancreatic cancer risk surveillance should be discussed.

(10) It should be stated that if they do carry an HP mutation, there is about a 20% chance that they will remain symptom free with normal pancreatic function throughout their life and with no added risk of developing pancreatic cancer.

(11) The person should be informed that there are possible adverse health and life insurance and employment consequences for an HP mutation carrier if these are not safeguarded against by national legislation.

(12) The person should be told that if they decide to proceed with predictive genetic testing, they must sign a consent form and then attend in person to receive their test result, i.e. that it will not be telephoned or posted to them.

(13) The person should be informed of the risks to their relatives of also carrying this HP gene mutation, and of their risks of developing pancreatitis.

(14) Whilst there are likely to be children at risk as a result of a positive genetic predictive test, we would discourage the offer of predictive testing to unaffected young people (see 'The Genetic Testing of Children' below).

(15) Discussion should take place regarding who else will be informed of their result, and who in their family they plan to tell.

(16) It should be discussed whether their test sample may then be used for any research project.

(17) If they do carry an HP mutation, the person should be informed of what further research is available in this and related areas that they might be interested in joining.

(18) The person should agree to a scheme for pancreatic follow-up if the genetic test result is positive.

(19) The person should also agree that they will come in person to receive their predictive test result, as it will not be given out by telephone, by letter or to another person.

(20) Arrangements should be made for the molecular genetic testing of their predictive test sample in an approved health service-funded or commercial molecular genetics testing laboratory with appropriate quality control standards.

The Genetic Testing of Children

We believe that children present special difficulties in the area of molecular genetic testing. Ill-conceived plans to screen children for HP mutations may have harmful psychological and practical consequences, as described above. This applies particularly to predictive testing, which can seldom be justified in children under the age of 16 years in the absence of a clinically proven intervention strategy. Children may need to be protected from both medical and indeed parental 'paternalism'. Certainly, individual and parental views must be taken into account when there are strong desires 'to know'. Anxious parents should be informed that genetic testing cannot predict the age of onset or the severity of the condition.

The age of 16 is somewhat arbitrary, but it is chosen as a watershed age. It will vary from family to family and from one culture to another. After the age of 12, we believe that a child can begin to contribute to the decision-making process, and should certainly be included. Only by their 'mid-teens' has the person developed sufficiently to understand the competing and lifelong implications of any decision. Before that stage, we would wish to postpone any decision until such time as we can protect that young person's autonomy. In most cases, the parents will be acting in the best interests of their child. Lifestyle modification is no reason to test children; advice to avoid alcohol use and smoking can be given to all at-risk children as well as children in the general population. Families with at-risk children are aware of potential HP symptoms, and it is emphasized that genetic testing can be performed if their child becomes symptomatic. Parents are encouraged to return for genetic advice when their chil-

dren are older or become symptomatic. Such decision making should be shared with a recognized genetic counselling service experienced in dealing with a range of genetic and predictive testing issues for families. This remains an area of individual judgement, influenced by local practice and culture. The phrase 'best interests of the patient' can be invoked here to guide decision making.

The diagnostic testing of an affected child is more straightforward. If a child of any age has presented with a well-documented episode of pancreatitis of unknown aetiology, then clearly HP is part of the differential diagnosis that needs to be excluded. We believe that the following are the indications for the molecular testing of a child (under the age of 16 years) for HP: (1) an episode of documented pancreatitis of unknown aetiology and severe enough to require hospitalization, or (2) two or more documented episodes of pancreatitis of unknown aetiology, or (3) an episode of documented pancreatitis occurring in a child where a relative is known to carry an HP mutation, or (4) a child with recurrent abdominal pain of unknown aetiology where the diagnosis of HP is a distinct clinical possibility, or (5) chronic pancreatitis of unknown aetiology where the diagnosis of HP is a distinct clinical possibility.

We are concerned that the availability of molecular genetic testing for PRSS1 mutations should not be used in general paediatric practice to screen all children with abdominal pain of uncertain aetiology and without evidence of pancreatitis.

Prenatal Testing for HP

We believe that the option of prenatal diagnosis should be presented as part of the general discussion of the genetic and clinical issues raised by HP. Assuming a culture of non-directive, non-judgemental genetic counselling that encourages decision making by the family, we as clinicians cannot decide for or against this by ourselves. It may be fair to say that members of a multi-disciplinary clinical and molecular laboratory team managing such patients may have reservations about the widespread offer of prenatal testing and ultimately the possibility of termination of pregnancy for HP. The reasons for this, and what should be discussed with a couple enquiring about prenatal testing, involve the following points:

(1) Research into HP is being actively pursued. There may be cautious optimism that interventions may be available in 10 years time that will offer more than the current supportive approaches.

(2) The family may have first-hand experience of HP and any decision that they ultimately make should be well informed and supported by the multi-disciplinary team (gastroenterology, pancreatic surgery, genetics, obstetrics) involved in their care.

(3) Continuing an 'affected' pregnancy would amount to having had a predictive test on the unborn child. We would wish to avoid this if possible.

(4) If the family are requesting prenatal testing, their reasons may be influenced by a severe case in their family and perfectly understandable concerns about the eventual development of chronic pancreatitis and the 40% lifetime risk of pancreatic cancer.

(5) The condition is variable, with incomplete penetrance. The genotype does not predict the phenotype. If a pregnancy is terminated there would be no way (currently) of telling if that pregnancy would have resulted in a child that would have been mildly or more severely affected or even unaffected.

(6) It should be pointed out that research protocols are being developed (EUROPAC) for screening patients with HP who are over the age of 40 and at risk of developing pancreatic cancer.

(7) Despite any reservations that we have, we believe that we cannot be so prescriptive as to refuse molecular genetic testing in an age of patient autonomy and informed consent. Otherwise we risk medical paternalism.

We emphasize again that this is an area where lengthy and specialized genetic counselling would be required.

Storing a DNA Sample

The approach to DNA storage will vary from centre to centre and may range from very open access to those DNA laboratories that are tightly regulated. The latter may have specific protocols and require documented informed consent. The position will vary from country to country, and even from laboratory to laboratory.

The Position in the United Kingdom

The United Kingdom Human Genetics Commission (HGC; http://www.hgc.gov.uk), formerly the Human Genetics Advisory Commission and the Advisory Committee on Genetic Testing, makes specific mention of proposals to establish large-scale (more than 500,000) collections of human DNA (http://www.medinfo.cam.ac.uk/phgu/newsletter/mrc_news_release.asp). The Icelandic government has passed legislation to offer its national 'genetic identity' to a for-profit research organization with-

out seeking individual informed consent [McInnis, 1999]. In their consultation document, the UK HGC (http://www.hgc.gov.uk/business_consultations.1.htm) comments that this represented an important subject requiring their early attention and that a discussion paper would be written on the complex legal and privacy issues surrounding this. The HGC ask 'what are the ethical, legal and social implications of greater use of gene sequence information for research, health care and commercial applications?' [see review by Morton, 1999]. The Nuffield Council on Bioethics has developed a discussion document on the issues regarding the use of human tissue in medicine, research and biotechnology (http://www.nuffield.org/bioethics/publication/humantissue/rep0013057.html).

The Clinical Molecular Genetics Society, the professional body representing all of the NHS-related DNA storage and testing facilities and some of those currently involved in medical genetics research, has issued position statements (http://www.rcpath.org/news/genetics/html) which are accepted as codes of practice. The UK Medical Research Council (MRC) has published guidelines on 'Human Tissue and Biological Research for Use in Research' for those working on MRC-funded research (http://www.mrc.ac.uk/tissues.html). This is alongside UK government advice to research ethics committees on the issue of genetic testing in research (http://www.doh.gov.uk/genetics/recrev3.htm). There are also comments on the Internet site of the Public Health Genetics Unit in Cambridge (http://medinfo.cam.ac.uk/phgu/), as well as links to further relevant Internet sites. However, there is no specific UK government legislation yet in the area of DNA storage.

The Position in Europe

The European Society of Human Genetics, drawing on a wide professional membership from across Europe, is looking at the issues of quality, confidentiality and informed consent in DNA storage and DNA banking [Earley and Strong, 1995] (http://www.eshg.org/PPRC.htm). A position paper on these issues by the German Society of Human Genetics (http://gfhev/kommission/eng/e_pospaper.htm) presents a thorough and representative view. Already, a European database on medical ethics has been developed to look at these matters (http://ww2.spri.se/scripts/spriweb.dll/ID?ID = I9304&lang = E), and a European course on ethics and genetics was arranged for November 2000 in Nijmegen, the Netherlands (http://www.azn.nl). However, inconsistencies exist between countries with different research, commercial and social agendas. Across Europe, there have been comments and disquiet about standards in fellow European countries [Rogers and Ashraf, 2000]. The Council of Europe opened the Convention on Human Rights and Biomedicine for signature in 1997. It contains principles for genetic testing and interventions in the human genome. In May 1999, the Council held a conference on the ethical implications of biotechnology, but no decision has yet been made on follow-up plans for this.

The Position in the United States

A profusion of statements have been published, including one by the American Society for Human Genetics [1996], on informed consent for genetic research. Annas and Elias [1992] have also published in this area. George Annas has proposed a Genetic Privacy Act for the United States (http://MED-SPH.BU.EDU/Depts/LW/DOCUM.HTm.z). This seeks to protect not just the DNA sample itself, but also the wealth of genetic analysis data that can result from it. Legislation has been suggested to regulate DNA data banks and even sources of biological material, for example blood banks in the widest context (see section 101 in http://ornl.gov/TechResources/Human_Genome/resource/privacy/privacy1.html). Extensive collections of discussion documents and position statements are being gathered (http://www.cdc.cov/genetics/Ethical.htm), and relevant texts in a bibliography on genetic privacy (http://www.ncgr.org/gpi/odyssey/privacy/priv_bibNZ90–95, html).

The International Consensus

The Human Genome Project has just announced its first draft (July, 2000). In parallel to molecular genetics analysis, there has been a decade of consideration of the ethical, legal and social issues by the Human Genome Organisation (http://www.nhgri.nih.gov/ELSI/). Of direct relevance to the issues discussed here is the *Statement on DNA Sampling: Control and Access* (http://www.gene.ucl.ac.uk/hugo/sampling.html). The statement emphasizes the need for respect for the person, in research using anonymous or coded samples, and data protection. Specific recommendations are made and a distinction is drawn between routine samples taken during medical care and research samples taken with consent specific for that research testing. Consideration for access by immediate relatives is made. In 1997, the United Nations Education, Scientific and Cultural Organisation adopted the 'Universal Declaration on the Human Genome and Human Rights', which is of moral, but not legal force (http://www.unesco.org/ibc/uk/genome/index.

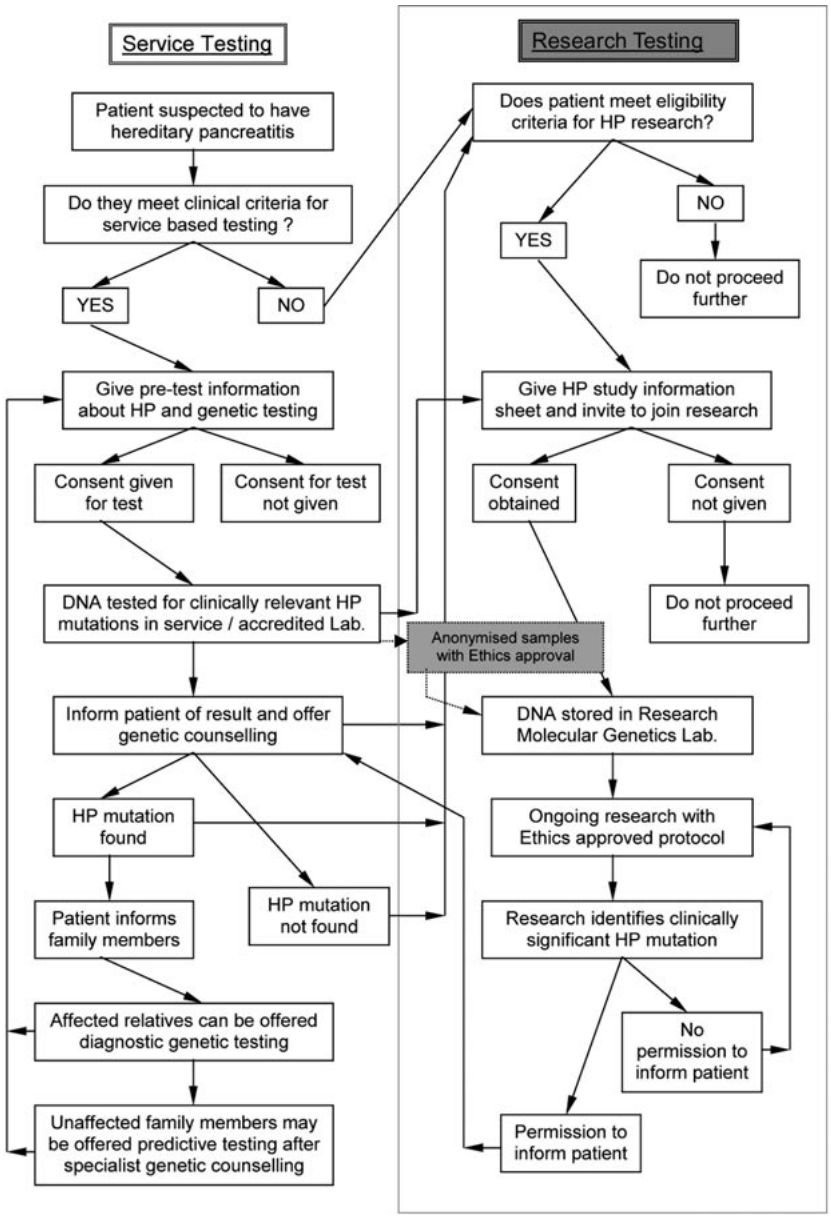

Fig. 1. Suggested model for handling service and research samples.

html). It is couched in the terms used by previous universal declarations of human rights and dignity, emphasizing, as many others have, the need for prior, free and informed consent. Information discussed at the time that DNA is stored may make reference to the following points.

(1) Description of where the DNA sample will be stored.

(2) The minimum time period for which that DNA will be stored.

(3) To whom does the sample itself and indeed the sequence information belong to?

(4) Who will be allowed access to that stored DNA sample?

(5) Can the sample be moved, shared or stored by any other DNA storage facility?

(6) If clinically significant findings arise from testing that DNA sample, who should be told and to whom should the results be given?

(7) In the event of the person's death, who will have ownership and decision-making rights over that banked DNA sample?

(8) Will medical doctors or specified researchers be allowed open access, and others only for a specified reason?

(9) Other uses to which that sample may be put, e.g. on an anonymous basis for research.

(10) Who will own any commercial benefits or patents that arise from DNA tests on that individual's genetic sequence?

The Transfer of Samples and Information between Service and Research Testing

The interface between service and research testing programmes is complex and potentially fraught with difficulties. Under no circumstances should DNA samples be taken casually from unaffected subjects. A genetic test result may inadvertently be disclosed, with dire consequences for the individual, his/her future, children and indeed the researchers. Technically, it can be viewed as an assault. Samples can be taken on the basis of non-disclosure of research results. These samples must be anonymous or the samples carefully coded so as to protect the identity of the individuals and to guard against the inadvertent release of unwanted genetic information. It is imperative that such samples obtained for research purposes are never used for clinical management and are never inadvertently disclosed. In this way, there should be no adverse insurance or psychological consequences. Figure 1 presents a suggested model for the separate handling of service and research samples, and the possible contact points between these routes.

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Appendix

The following authors contributed to the above consensus statement at the Third International Symposium on Inherited Diseases of the Pancreas (www.inherited-diseases-pancreas.com), Milan, Italy, April 5–7, 2001 (in alphabetical order):

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