The Use of Biological Sample Collections and Personal Medical Information in Human Genetics Research

By Paul Martin and Jane Kaye

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Introduction to this Paper and the Workshop

This paper is intended as a background briefing and discussion document to provide an overview of the field for participants in the Wellcome Trust's workshop on *The Collection of Human Biomedical Samples*. The Trust commissioned the paper from Paul Martin, a sociology lecturer and research fellow at the University of Nottingham, and Jane Kaye, a lawyer currently carrying out research into DNA banking at the University of Oxford. It is not intended to provide a definitive statement of either the scientific or of the legal, social, ethical and public policy issues arising from developments in this field.

The purposes of this paper are to provide description and some exposition of regulatory and legal aspects of biological sample collections and personal medical information in research, and to raise some of the social, ethical and public policy questions which might be generated by recent developments.

Addressing the questions that arise from this paper will require research and analysis. It is hoped that the workshop will prompt participants to think of more research questions and to devise appropriate research methodologies. The workshop is not intended to debate issues, but rather to start asking research questions. Ultimately, the hope is that the results of research and analysis might feed into rational public policymaking.

Any views expressed in this paper are solely those of the author and do not necessarily represent those of the Wellcome Trust or any of its affiliates. The Wellcome Trust takes no responsibility for any factual errors within this document.

Tom Wilkie,
Head, Biomedical Ethics
27 October 1999

The Wellcome Trust
183 Euston Road
London NW1 2BE, UK
Tel: +44 (0)20 7611 8888
Fax: +44 (0)20 7611 8545

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- Issues for Social Science Research and Public Policy

Paul Martin and Jane Kaye

Background paper for Wellcome Trust workshop on *'The Collection of Human Biological Samples for DNA and Other Analysis'*. London 5th November, 1999

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Paul Martin is lecturer in the School of Sociology and Social Policy and research fellow at the Genetics and Society Unit, University of Nottingham. Paul.Martin@nottingham.ac.uk.

Jane Kaye is a lawyer and is currently carrying out doctoral research into DNA Banking using Iceland as a case study, at the University of Oxford. Jane.Kaye@law.ox.ac.uk.

1. Introduction

The issues raised by the increasing use of large-scale biological sample collection for genetic research are profound. They touch on critical issues of human rights, personal identity, the future conduct of biomedical research, new forms of property rights and the proper relationship between academia and commerce. At the same time, and partly in response to these new scientific developments, public policy is in the process of transition. The MRC and the professional bodies are currently formulating new guidelines relating to the conduct of medical research, and important legal rulings affecting this area are pending. Some of the issues raised by sample collections will be considered by a House of Lords Science and Technology Committee inquiry due to start later this year. However, it seems highly likely that further important policy initiatives in this field will be taken at both national and European level in the coming months.

As a consequence, this paper has been written at a time of uncertainty and change, and its analysis and conclusions reflect this. Furthermore, the technical complexity of the scientific research in this field and the rapid pace of change make it difficult to present some of the developments in a manner which is both accurate and easily understandable to a non-specialist audience. The law relating to this type of research is also complex, and at times contradictory, and is not easily amenable to a brief description. Every effort has been made to provide enough technical, scientific and legal background to the issues raised by the use of large sample collections, but this has perhaps been at the expense of brevity. It is hoped that the organisation of the paper will both guide the reader across this difficult landscape and stimulate ideas for discussion and further investigation.

The paper has therefore been written with a number of aims in mind. Firstly, it will attempt to briefly describe the scientific research strategies in the emerging field of functional genomics and the way in which investigators are using biological sample collections, genealogical data and personal medical information to hunt for gene-disease associations. In particular, it will be shown that the use of sample collections cannot be easily separated from the use of medical records and data about family relationships. This is a fundamental point raised by the paper and one that runs throughout its structure.

The role of the biotechnology industry will also be briefly considered. Much ethical analysis of the issues raised by new genetic technologies is carried out in a social and economic vacuum, often without reference to the objectives of the powerful social actors who shape the field of research. In the case of biological sample collections, it is likely that industry will play a major role in the development of this field. A complete analysis of the issues raised in this area must therefore be contextualised by understanding both the aims of the biotechnology industry and the nature of the very close links being forged between academia and commerce.

Following the introduction of the scientific and commercial background, a series of case studies of research involving the use of large biological sample collections and personal medical information will be presented. Much of the recent discussion of sample collections has been sparked by developments in Iceland and the activities of the biotechnology

company, deCODE Genetics. The Icelandic situation will be described in some detail as it provides the best example of large-scale research of this kind, the broad social, ethical and legal issues raised and the policy response to these concerns. Some examples of current or planned research in the UK will then be briefly presented to highlight the key issues raised in the British context.

Many of the concerns being expressed about the potential misuse of the genetic information being generated by genomics research relate to the adequacy of the legal framework governing the conduct of investigation. The ownership of biological samples and genetic information also raises other important issues. The third section of the paper will therefore present the current UK legal framework relating to the ownership of biological materials, patient confidentiality and consent. Important points about the adequacy of the existing legal framework in the light of new types of genetic research will be highlighted.

Finally, the key issues for further discussion and areas for future social science research which follow from both the case studies and the review of UK law will be summarised in the concluding section. It must be stressed that this background paper is not meant to be definitive in its considerations of the issues surrounding the use of biological sample collections and personal medical information, but it is hoped it will stimulate debate and further work on this important topic.

2. Genetic research involving large biological sample collections

This section will first aim to present the scientific thinking behind studies linking diseases to particular human genetic variations. There are a range of diverse strategies and techniques being adopted in this area. Only by understanding the different technical rationales for the use of tissue sample collections and personal health information is it possible to analyse the full range of ethical, social and legal issues raised by this type of research. The section will then go onto examine the growing commercial interest in this area and the types of firm strategies involved. It is very likely that the biotechnology and pharmaceutical industry will be at the forefront of developing DNA banking and it is therefore highly relevant to understand their objectives in this respect.

2.1 Technical background and rationale: functional genomics

2.1.1. The post genome sequencing research agenda

One of the landmarks in modern biology is due to be reached in the next few years when the sequencing of the entire human genome will be completed. This goal is embodied in the international Human Genome Project (HGP), the first phase of which is due to finish two years ahead of schedule in 2003[1]. In the UK, the Wellcome Trust has made a major contribution to this project by funding the Sanger Centre, which will provide a third of the total sequence data. However, the sequencing of the genome is only the start of a major programme of research, which is likely to occupy the biological sciences for decades to come. The next stage of investigation will be to understand exactly what the information coded in the human genome means and how this new knowledge might be used to improve health and healthcare.

Central to this task is the need to establish the function of the 100,000 - 140,000 genes contained in the 23 pairs of human chromosomes. At present, the biology of the great majority of the thousands of genes that have already been sequenced is unknown. Although the proteins which they code for can be identified, their role in both the normal workings of the body and in pathology is much harder to identify. Until the function of a particular gene and its role in pathology has been established, the raw sequence information is of little clinical value. This area of research has become known as functional genomics and is one of the most rapidly expanding areas of molecular biology.

The research required to link gene sequences (genotypes) to particular biological functions or diseases (phenotypes) is complex and involves a series of steps. Historically, the first studies in this area were based on the analysis of what have been called inherited monogenic disorders, such as cystic fibrosis. In these rare diseases, the pioneers of clinical genetics

[1] Collins, F. *et al* (1998) New Goals for the US Human Genome Project: 1998-2003. Science, 282, p682.

identified simple patterns of family inheritance. These were then related to the inheritance of particular chromosomes, or regions of chromosomes, using classical techniques that predated the advent of recombinant DNA.

Until recently, researchers have worked 'backwards', starting with the identification of an inherited pattern of a disease and then trying to find the genetic changes responsible for the condition. In some examples, such as haemophilia, the biochemical basis of the pathology could be readily identified - in this case a change in blood clotting proteins (Factors VIII and IX). The gene coding for Factor VIII could then be 'hunted' using a combination of traditional genetic mapping techniques and crude gene sequencing.

However, in most common diseases the biological changes responsible for the pathology are not well characterised or it is difficult to demonstrate a simple pattern of familial inheritance. As a consequence, scientists have adopted a working hypothesis that some diseases, such as asthma, have a genetic component. Research then involves trying to make a correlation between having the disease and carrying a particular gene sequence or genetic change.

This type of research is made more difficult by the fact that only a sub-set of some common diseases may have a clear genetic component to them. In the case of breast cancer it is now clear that a sub-population of 5-10% of all cases is largely due to the inheritance of mutations in the BRCA I and II genes. The remaining 90% of breast cancers appear to be mainly caused by environmental factors, and even the presence of a BRCA mutation does not guarantee that a woman will develop the disease. The challenge for researcher is therefore to try to identify which sub-groups to study in large populations of people suffering from a given disease. In the case of familial cancer this is fairly straightforward. However, in other diseases, where there is no clear pattern of inheritance, this is a demanding task as the starting assumption may be incorrect - there may simply be no significant genetic component!

Another closely related area of research is the study of pharmacogenetics, which attempts to identify the genetic basis of adverse drug reactions (ADRs). Initial studies suggest that up to a third of patients given drug therapy may suffer some form of ADR and that in a number of cases this may have a genetic basis. If patients could be screened before starting drug therapy, it might be possible to avoid administering a harmful medicine, thus increasing the overall efficacy of the treatment. In this type of research, the DNA of people who have suffered an adverse reaction is compared to those that haven't reacted to treatment, in the hope that a particular gene sequence can be identified which is unique to those suffering the ADR. This can then act as a 'diagnostic' marker to modify treatment regimens.

In summary, the overall research agenda in this area is shaped by four related questions:

- Is it possible to identify (sub-populations of) common diseases which show some pattern of inheritance and might therefore have a genetic component?

- How can the gene sequences responsible for (sub-populations of) an inherited disease be identified?

- Is it possible to make a correlation between a disease (or adverse drug reaction) and a specific genetic change in cases where no pattern of inheritance is obvious?

- How can the complex interaction between environment factors and specific (groups of) genes, which cause most common acquired diseases, be studied?

The first three of these questions belong to the realm of molecular genetics and the fourth to what has become known as 'genetic epidemiology'. Each of them will be discussed briefly below.

2.1.2. Identifying diseases which show patterns of inheritance

The starting point for most research aimed at identifying diseases which have an inherited component are studies of families or small groups where there is evidence of a higher than average incidence of a particular condition. Family studies of this sort have been routinely undertaken by clinical geneticists in the UK, and include research on rare monogenic disorders, familial cancers and familial forms of other common diseases. As part of their work they have constructed banks of tissue samples from affected people, as well as family pedigrees charting the inheritance of the condition across generations. These types of resources have provided the basis for much of the early work in this area and have become valuable research commodities. In these cases, where the inheritance of the disease is well-characterised, relatively small numbers of subjects/ samples are required for analysis and little additional clinical information is needed beyond a positive diagnosis for the condition.

However, relatively little work has been done on the inheritance of more common diseases. In order to investigate if some diseases previously thought of as being acquired have inherited forms, researchers have recently started to hunt for small groups or populations that appear to suffer from a high rate of a given disease. Such communities may often be geographically isolated, resulting in a level of inbreeding and genetic homogeneity which makes genetic studies easier. Two well-known examples of this are work carried out on the remote south Atlantic island, Tristan da Cunha, and on Iceland. Tristan da Cunha's tiny population is descended from a small group who settled in the 1800s, and nearly a third of its inhabitants suffer from a form of asthma. Family groups with inherited patterns of asthma were identified and blood samples taken from the population by a team of Canadian clinicians working with the US firm Sequana (now Axys)[2]. Sequana has also collected samples from other communities and families with high incidences of asthma in the Brazilian highlands, China, Australia and California[3]. The company has subsequently announced the identification of a genetic change closely associated with the development of asthma in these groups.

In the case of Iceland superb genealogical records exist which greatly extend the scope of this approach. It is claimed that some 650,000 of the 800,000 Icelanders who have ever lived are catalogued in the countries genealogical archives. An Icelandic biotechnology firm,

[2] Marshall, E. (1997) Whose DNA is it Anyway? Science, 278, p564-567.
[3] (Ibid.)

deCODE Genetics (see below), is creating an electronic database of these records which enables patterns of inheritance to be studied throughout the population. Using this tool, people who may at first appear unrelated can be traced back to a common ancestor, thus enabling the construction of highly extended family pedigrees. The power of this approach is well illustrated by a study the company undertook of all Icelanders over the age of 90. Extended family trees were created using genealogical records and it was found that the distribution of 90-year-olds was not random. Instead, it appears that this group were much more closely related than would have been predicted, pointing to a common ancestry and the inheritance of a small number of 'longevity genes'. deCODE has already successfully used this approach to identify an inherited form of susceptibility to pre-eclampsia.[4]

Through the use of family, group, and genealogical studies it has become possible to identify sub-populations of relatively common diseases that have a clear genetic component. Many of these conditions had not previously been thought of as 'genetic' in any sense. However, it must be stressed that it is far from clear what causes the disease in these cases, as environmental triggers may always be required for the onset of conditions such as asthma. It may be that some forms of common diseases are closely associated with the possession of a particular genotype, whilst other forms are purely environmental. Already, asthma and diabetes are being reclassified into different sub-types, some of which are strongly influenced by genetic factors.

In these cases it is perhaps more useful to think of genes as being risk factors. If a person has a particular genotype they may be more at risk of getting a disease than people not carrying that specific genetic change. However, it is far from clear if the possession of a gene variant will automatically lead to the development of the pathology. Even in some classic monogenic disorders, such as Gaucher's disease, identical twins with the same genome may different in their response, with one twin suffering from the disease and the other remaining healthy. Some genes may only be partially 'penetrant', that is, only in a certain percentage of cases will a person carrying the gene get ill. In other situations the disease may only be caused by the interaction of a gene with specific environmental hazards. In each of these examples genes can be said to be associated with an increased risk of getting a diseases, but the causal mechanism of pathology may differ fundamentally.

2.1.3. Identifying the gene sequences associated with inherited diseases - linkage studies

Where a clear pattern of inheritance of a disease can be established, powerful genetic mapping techniques can then be used to identify the genetic changes (mutations, deletions, polymorphisms etc) which are associated with the pathology.

Instead of studying the total human DNA sequence, analysis is simplified by examining a relatively small series of short DNA marker sequences spread evenly across the entire genome (a process known as genotyping). The pattern of inheritance of these marker sequences is then related to the pattern of inheritance of the disease within the families

[4] Arngrimsson, R. et al. (1999) A genome-wide scan reveals a maternal susceptibility locus for pre-eclampsia on chromosome 2p13. Human Molecular Genetics 8(9), p1799-18-5.

studied. Using this approach it is possible to identify particular small regions of chromosomes which contain the genetic change associated with the condition. Further detailed mapping can then be undertaken using a finer mesh of genetic markers covering the particular region of interest. Finally, automated gene sequencing and the use of gene sequence databases can then be used to identify the possible genetic change involved.

Once a set of putative gene sequences which might be involved in causing the disease have been identified, the DNA of affected family members can then be screened to detect the presence of specific genetic changes. Unaffected family members are used as a control group throughout this research, thus enabling the identification of genetic changes which appear to be unique to people with the disease. Further work can then be undertaken to validate the findings. In the case of asthma, for example, the result might be made more credible if the genetic changes involved could be shown to be in a gene associated with the working of the lung airway.

It should be stressed that these types of linkage studies are restricted to cases where a familial pattern of inheritance has been clearly established. In more complex situations, where a genetic change may only increase the susceptibility of a person to a disease, a different approach has to be taken which requires far bigger sample collections and more detailed clinical information.

2.1.4. Making a correlation between a disease and a specific genetic change in cases where no pattern of inheritance is obvious - association studies

The basic principle behind genetic association studies is the statistical correlation between specific DNA sequences and particular diseases. As a consequence fairly large groups of people suffering from the disease have to be studied, as only a sub-population of the pathology may involve a strong genetic component or, alternatively, the genetic influence could affect many people, but may not be very marked.

Instead of trying to make diseases-gene associations using raw sequence data, researchers are starting to use single nucleotide polymorphisms (SNPs). It has been found that human populations are to some extent genetically heterogeneous; i.e. the exact sequence of a particular gene varies within a population. The variation is generally limited to a relatively small number of single base pair changes (SNPs) which are stable and inherited across generations. Many of these SNPs are not harmful (e.g. some cause the different blood groups A, B, O, AB), but some appear to be deleterious and may be involved in causing specific diseases or adverse drug reactions.

The hunt for SNPs is currently a major area of investigation. It has also been surrounded by controversy after the recent formation of Celera Genomics by Craig Venter, which has announced plans to sequence the entire human genome in three years as a means of identifying and possibly patenting SNPs. A number of other leading genomics companies are also involved in the patenting of SNPs. Although it is unclear if investigators can protect SNPs by patents, this prospect has unsettled many in the scientific community. One response to the ownership of large polymorphism maps by private companies, has been the formation

of the SNP Consortium. This initiative is led by the Wellcome Trust and involves leading academic gene sequencing centres and ten major pharmaceutical companies. It has a budget of $45 million over two years and aims to identify up to 300,000 SNPs and map at least 150,000 that can be used in association studies. The information will be placed in the public domain, allowing unrestricted access by the international research community.

The overall strategy guiding association genetics involves collecting samples from patients with a specific disease and then genotyping their DNA using large arrays of SNP markers. The hope is that specific SNPs will be found to closely correlate with the disease being investigated. This analysis is also carried out on individuals not suffering from the disease, to provide a control group. This is a technically very demanding procedure involving high speed DNA screening on a huge scale, coupled to complex statistical analysis using massive data processing. It is still in its early stages of development and it is not yet possible to carry out an SNP scan of the whole genome.

However, searches can be narrowed in two ways, allowing them to be undertaken with existing technology. Firstly, analysis can be done of small sets of SNPs in genes or chromosomal regions of interest. Secondly, they can be focused by using more demanding clinical criteria to select the patient population for analysis. This is important, as a single polymorphism may either result in a range of phenotypes (clinical symptoms) or be responsible for only a sub-set of symptoms. Highly accurate clinical data that profiles the full range of symptoms therefore has to be used in the analysis, demanding access to the full patient history and their medical records.

The same broad approach can also be used in pharmacogenetics for the identification of the genetic basis of adverse drug reactions (ADRs). The only difference is that the patient population is selected from people who have received drug therapy and experienced some form of ADR. As with the use of association genetics for the study of disease, this requires relatively large sample collections, careful controls and detailed clinical information.

Once an association is made between a specific polymorphism and a disease phenotype, the biology of the gene sequence can then be studied using other techniques to validate the finding. Alternatively, association studies can be used to study the SNPs that occur in, or close to, genes that are already known to be involved in causing disease. This might enable greater insight into pathology, and could also help expand the range of indications for drugs targeting the gene product.

2.1.5. Studying the interaction between genes and environment - genetic epidemiology

In recent years, new fields such as 'genetic epidemiology' and 'molecular epidemiology' have emerged which seek systematically to apply the traditional methods of epidemiology to the study of environment-gene interactions and their role in pathology. As greater knowledge of genes associated with diseases and human genetic polymorphisms is gained, it will be increasingly possible to analyse the role which genetic risk factors and specific environmental hazards play in the cause of common conditions such as cancer or heart disease.

Research strategies for genetic epidemiology are still being developed and no large-scale study has yet been established in the UK. However, it is clear that this type of research will depend on very large population-based sample collections and access to detailed patient information (i.e. medical records). It may also involve longitudinal studies, which have a prospective element to them; i.e. in which predictions made on the basis of genomic information are tested at a later date. Although there is little direct commercial interest in this area, a number of government agencies in the US and the UK are currently considering establishing large-scale tissue collections for this purpose.

In summary, although the genetic research strategies described above all use human biological samples there are important differences in the type of samples collected, the scale of the collections, the extent to which they are integrated with personal medical information and the time period over which research takes place. These differences are shown in Table 1.

Table 1. Genetic research strategies involving biological sample collections

Strategy	Family or genealogical studies	Type of sample collection	Medical information required	Time period
Linkage studies	Yes	Family collections	Only limited information essential	Historical
Association studies of disease	No	Large population of people with a given condition	Fairly detailed - information on full range of symptoms	Historical
Pharmacogenetics	No	Collection of people suffering from ADRs	Fairly detailed - information of drug therapy and ADRs	Historical
Genetic epidemiology	No	Very large population collections	Detailed information on patient history	Historical/ prospective

2.2. The use of human biological sample collections by the biotechnology and pharmaceutical industry

2.2.1. The potential industrial use of functional genomic information

A gene sequence alone is generally not enough to be useful to industry, as firms need to know what the gene does and how it might be used in the development of therapeutics and diagnostics. Data about the biological function of genes and the association of specific polymorphisms with diseases is useful in the development of a number of technologies:

- *Target validation* - confirmation that a particular gene is a useful target for the development of conventional small molecule drugs;
- *Pharmacogenetics* - identifying the genetic basis of (adverse) drug reactions;
- *Diagnostics* - by linking a particular genetic variant with a given disease it may be possible to develop pre-symptomatic genetic tests;
- *Therapeutic proteins* - if a gene's function in pathology can be clearly established, it may be possible to use the gene product (protein) as a therapeutic;
- *Gene therapy* - if a gene's function in pathology can be clearly established, it may be possible to use the direct application of the gene as a therapeutic.

2.2.2. Firm strategies in functional genomics

The majority of firms working in this area are primarily concerned with generating and selling information about the relationship between specific genetic sequences and particular diseases or ADRs, rather than developing drugs themselves. However, some firms are planning to develop diagnostic tests based on this data, a number are offering contract genotyping services, and others are looking to develop drugs in partnership with large pharmaceutical companies.

Table 2 gives information about the strategies of some of the leading European biotechnology firms working with large sample collections. It illustrates the mixture of strategies being adopted by firms, with the main focus on the hunting of genes associated with common diseases and studies of pharmacogenetics. The most popular disease targets include cancer, cardiovascular diseases, depression, schizophrenia and osteoporosis.

It should also be noted that research is international in scope, with companies working in many countries across different continents. For example, Genset is working in Ireland in collaboration with clinicians who have access to samples from more than 10,000 patients who have suffered from cardiovascular diseases. It is also collaborating with doctors in both Israel and Argentina to build sample collections from families suffering from particular diseases. The biggest sample collection in Europe is held in Sweden and contains over 3 million samples in a single repository. It is being exploited by Eurona Medical.

Although Table 2 describes the leading dedicated functional genomics firms in Europe, many leading pharmaceutical companies now have major interests in the collection of biological

samples. Specifically, there has been a rapid growth in pharmacogenetics research in recent years, with companies increasingly taking samples from participants in clinical trials as a means of identifying the genetic basis of ADRs. Relatively little is known about the scale of these collections by large pharmaceutical companies, but industry reports suggest that this is now a routine activity. In the UK Glaxo Wellcome has been involved in this practice for some time and has changed its procedures to widen the scope of consent obtained from patients in trials. The company also has a significant interest in association genetics after its acquisition of the US firm Spectra Biomedical.

In should be highlighted that private sector activities depend heavily on both public funded research and widespread public participation. It is therefore difficult to disentangle public and private research, as researchers from both sectors are often involved in supporting the same project. Very close academic-industry links are a general feature of research in human genetics. Whilst this enables effective technology transfer, it also gives rise to concerns about academic conflicts of interest.

This section has highlighted the heavy commercial involvement in genetic studies using large sample collections, however, it must be stressed that significant public sector initiatives have also been established in a number of countries and many academic groups are working in this area. Examples of some of these projects will be described in the next section.

Table 2. Strategies of selected European firms working with large sample collections

Firm	Business focus/ disease areas	Scientific strategy	Samples collected	Personal medical information used
deCODE Genetics (Iceland)	Identification of genes linked to common diseases. Pharmacogenetics. Sale of data and development of diagnostics. 35 disease targets (see below)	Linkage and association studies (SNPs)	10,000 samples taken from Icelanders with specific diseases	Use of limited data about disease at present. Planned used of comprehensive database of all population's medical records
Eurona Medical (Swe)	Pharmacogenetics. Sale of data, related diagnostics and predictive tests. Hypertension, cancer, depression and schizophrenia	Location of genetic variants associated with ADRs	Access to over 3 million samples and related medical records	Data about therapy, outcomes and adverse reactions
Gemini Research (UK)	Identification of genes linked to common diseases. Sale of data and development of diagnostics. CV disorders, obesity, osteoporosis	Association studies (SNPs)	Collection of samples from several thousand non-identical twins	Very detailed clinical information (over 900 data points) - much collected during research
Genset (Fra)	Identification of genes linked to common diseases. Pharmacogenetics. Sale of data and development of diagnostics. Cancer, schizophrenia, depression, Alzheimer's, obesity, CV disease, osteoporosis	Linkage and association studies (SNPs). Location of genetic variants associated with ADRs	Access to collections in USA, Israel, Argentina, France, and Germany. Irish collaboration using >10,000 samples from CV disease patients	Varies according to study, but would involve access to full patient records in several cases
Oxagen (UK)	Identification of genes linked to common diseases. Pharmacogenetics. Sale of data and development of diagnostics. Osteoporosis, endometriosis, inflammatory bowel disease, coronary artery diseases	Linkage and association studies (SNPs).	Families with high incidence of disease. Studies planned with samples from up to 10,000 individuals	Use of limited data about disease at present. Planned development of large database of genotypes and outcomes

3. Case studies relating to the use of biological sample collections and personal medical information in human genetic research

A series of case studies will be presented in the following sections to provide concrete examples of the type of research being undertaken and the ethical, social and legal issues raised by these developments. The first example will be the work of deCODE Genetics in Iceland and the creation of the Icelandic Health Sector Database. This will be followed by brief descriptions of some examples of current or planned research in the UK.

It is essential to be clear that one fundamental concept in this arena is protecting confidentiality for those about whom personal medical data is collected. There is great confusion about the three technical fixes that can be employed to enhance confidentiality: anonymity; encoding; and encrpyption. Many commentators appear to use the terms interchangeably, which causes confusion as they refer to different procedures. The following demarcation is suggested, but instances may be found in this report where the terms are inadvertently interchanged.

- Data can be made ***anonymous***, if all information capable of identifying the individual to whom the data relates is removed and destroyed. Further information pertaining to that individual could then never be added to the appropriate record in the database, because the individual's record is not identifiable by anyone.

- Data can be ***encoded***, if a serial number or other code is attached to data and a key to this is held elsewhere. Encoded data might be effectively anonymous to the research team working on it because they do not hold the master-list which links the serial numbers to names and addresses, or other personal identifiers. However, the data would not be truly anonymous as someone would be able to link the two. Encoding would allow updating of an individual's record, e.g. in the course of a longitudinal study or to incorporate information about disease in their close relatives.

- ***Encryption*** means turning data into meaningless strings of numbers or letters. Only someone with the key can decipher the record itself (which may, or may not, contain personal identifiers). Encryption may be useful not so much for reasons of confidentiality towards the data subject as for reasons of commercial security, to prevent unauthorised access by rivals to commercially significant collections of data.

Public discussion of the Icelandic databases has used the terminology of anonymisation but it is not clear how the separate databases can be linked to yield scientifically useful information if the data is truly anonymous rather than merely encoded (see sections 3.1.5, 3.1.6, 3.1.7).

3.1. deCODE Genetics and the creation of the Icelandic Health Sector Database

Much of the recent international discussion of the issues raised by the use of biological sample collections has been stimulated by developments in Iceland. In particular, a proposal for an electronic database containing detailed information from the entire population's medical records has been championed by a biotechnology company, deCODE Genetics. This has aroused widespread fears about the potential abuse of human genetic research. Some of this debate on events in Iceland has been poorly informed, so the following sections will therefore set out the Icelandic situation in some detail.

3.1.1. deCODE Genetics and its scientific strategy

deCODE Genetics is a private company founded in 1996 by Kari Steffansson, an Icelander who was previously professor of neurology at Harvard University. The firm operates out of Reykjavik and employs nearly 300 staff, a majority of whom are Icelandic. Although deCODE is registered in Delaware, USA, over 70% of its equity is now owned by Icelandic investors.

The company was created specifically as a 'population-based genomics company conducting research on the causes of common diseases'. In particular, it aims to exploit unique features of Iceland's population, as well as the country's extensive genealogical records and high quality healthcare system. Most Icelanders are descended from a very small number of individuals who settled the country in the 9th Century. This has resulted in a high level of genetic homogeneity. As a consequence, Icelanders are likely to have fewer variants of genes involved in causing a given disease than might be found in more heterogeneous populations. This greatly simplifies the technical problem of trying to identify these disease-related gene variants by reducing the signal to noise ratio.

In order to carry out the genetic analysis of common diseases the company has established two core technologies:

> *A computerised genealogical database* - containing records of 600,000 individuals (living and dead) and their family relationships. Records on the database used for research are coded and are not identifiable by name (see below).
>
> *High-throughput genotyping* - the ability to process and scan DNA samples using large numbers of genetic markers, such as tandem repeats and SNPs. This allows it to perform both high-resolution linkage and association studies.

The first phase of the firm's research strategy, which has been underway for several years, has been based on collaborating with local doctors to collect DNA samples from people suffering from particular diseases. The genealogical database is then used to cluster these patients into large extended families, thus allowing genetic linkage analysis to be undertaken using high throughput genotyping. As of September 1999, the company had collected samples from over 10,000 people with full written consent. Further details of the organisation of this research are given in section 3.10.

By 1999 deCODE had already established research programmes on the genetics of 35 common diseases, including cancer, myocardial infarction, heart disease, multiple sclerosis, diabetes, osteoarthritis, Alzheimer's disease, schizophrenia, and bipolar disease. Twelve of these programmes are in collaboration with the pharmaceutical company Hoffmann-La Roche, who is paying $200 million over five years for access to the findings.

The second phase of the firm's research strategy will involve the construction of an electronic health information database, the Icelandic Health Sector Database (IHD), which when built will contain the encrypted medical records of almost the entire population. Work has not yet started on this and it is not likely to be complete for several years. The estimated cost of building the database could be as much as $150 million and its creation is therefore subject to funding being raised by the company.

The right to construct and operate the IHD will be licensed from the Icelandic government, which has passed specific legislation on this matter (see below), and it will be financed entirely by the company. In return, deCODE will have the sole right to exploit this resource commercially for a period of 12 years.

deCODE's overall business strategy is based on creating services and products derived from both elements of its research strategy. These would be sold to large pharmaceutical companies and biotechnology firms, and might initially include:

- Searches for genes associated with particular diseases and adverse drug reaction
- Access to 'depersonalised' health data from the IHD, which would be sold in the form of a non-exclusive subscription
- Genetic testing
- Research equipment and software

However, if the company is successful, this list of services and products might be significantly extended.

3.1.2. The proposal for the Icelandic Health Sector Database

The proposal for the IHD contained the following elements:

- The database would contain personal medical information on all citizens and would be based on their medical records;
- The information would be held in an anonymous form that would prevent the identification of individuals;
- The right to build and operate the Database would be licensed by the government for a fixed period;
- Its operation would be carefully regulated through the licensing agreement and a series of government agencies;
- The Database would not be linked to other external and unrelated databases but will comprise the three related datasets (the genealogical database, medical records and genotyping data).

According to deCODE the IHD will contain information on:

- 'Longitudinal disease progression
- Treatment and treatment response
- Direct and indirect cost of treatment and cost effectiveness'[5]

This main emphasis would be on health related data which can be coded and would include medical information, health resource use, genealogical information and genotype data. Diagnoses, test results, data on forms of treatment, side-effects, response to treatment, duration of therapy, and place of treatment would all be entered, allowing costs to be calculated. Other relevant information that could be coded will be included, but no medical records in text form will be entered on the Database.

The potential use of the Database is described by deCODE: 'When coupled with genealogical and genetic data, the genetic pattern of various diseases can be elucidated further, as well as the relationship between genetics and pharmacological response.'

'The opportunities created by this approach will allow for the following:

- Assisting healthcare providers in tailoring the treatment to individuals according to the genetic basis of disease and treatment response;
- Enabling healthcare providers and payers to analyze and single out the most cost-effective treatment for various diseases, …;
- Constructing models for developing disease management programmes;
- Providing pharmaceutical researchers the chance to use both a macroscopic and microscopic approach to understand the origins of complex diseases and find more specific drug targets.'[6]

However, as of October 1999 many details of the Database were still unresolved including, exactly what information it will contain, how it will be used and if all these planned applications would be possible. Further details of the IHD and how it might be used specifically in genetic research are given below in section 3.1.11.

3.1.3. The public debate on a Health Sector Database

The proposal for the Health Sector Database has been highly controversial both in Iceland and internationally. Over the past eighteen months there has been considerable debate in the Icelandic Parliament (the Alpingi), in the electronic media and press concerning its creation. Icelandic groups opposed to the plan, such as Mannvernd and the Medical Association have galvanised international criticism of the proposal and the world's media have led with headlines such as the 'Selling the family secrets'[7] and 'A human population for sale.'[8]

[5] www.decode.is
[6] www.decode.is
[7] *New Scientist* 5th December 1998
[8] *New York Times* 23rd January 1999

The Database has been controversial for a number of reasons, including:

- The legislation was drafted quickly and without wide spread community consultation, and there were rumours that deals had been done behind closed doors.
- The original proposal did not allow people the opportunity to consent to the use of their personal information and did not allow them to opt out of the Database. This has since been changed, as people now do have the opportunity to opt out within a fixed period;
- The original proposal was to encode the medical records rather than make them anonymous, which meant they could more easily be traced back to individuals. In a small country like Iceland this would have major implications for privacy;
- There were fears about the security of such a database;
- The Icelandic scientific community was worried about scientific freedom and the effect on research of putting access to medical records in the hands of a private company;
- The fact that the personal information of a whole population was to be collated by a private company, with no clear statements as to how the Database would be used, was alarming;
- There was scepticism about the promised benefits to Iceland and concern that a single company was been given a potentially lucrative monopoly.

In addition, the international research community had wider concerns, including:

- Research done unethically in Iceland would tarnish the image of genetics research across the world;
- Genes were being exploited for private profit;
- Parliament was acting with little regard for human rights or ethical principles.

The Icelandic Parliament attempted to address these public concerns and the criticisms of the original proposal by redrafting the Health Sector Database Act. Furthermore, the regulations that will govern the establishment and running of the Database are still in the process of being drafted and their details will be crucial in meeting the concerns of opponents of the plan. The fact that many of the details about the Database are still undecided means that Iceland will continue to be a focus of world attention.

3.1.4. How the Icelandic Health Sector Database will operate

In December 1998, the Icelandic government passed the Act on a Health Sector Database 1998[9], allowing the creation of a centralised database from the medical records of the entire Icelandic population, generated through the national health service. The Act allows a license to create and operate the Database to be given to a private company. This is almost certain to be granted to deCODE Genetics.

[9] No. 139/1998 Passed by Parliament 22 December 1998, at the 123rd session, 1998-99

In particular, the Act specifies that:

- The Health Sector Database will be used for epidemiological studies[10];
- Individuals 'can not benefit directly from specific information concerning them.'[11];
- The Icelandic government can gain information to assist in the planning of healthcare provision and services;
- deCODE Genetics will get the exclusive right to exploit the database for 'financial profit'[12] for a period of 12 years.[13]

While the legislation has been passed, many of the requirements for operating the Database have still to be finalised. For example, at the end of September 1999, the regulations determining how the Database will run had still to be formulated; the Monitoring Committee overseeing many of the contractual agreements was still in its infancy; and the license to set up and operate the Database had still not been granted.

Like many small nations, Iceland does not have the financial resources to develop such a database without private investment. The Health Sector Database Act 1998 therefore requires that deCODE Genetics bear the costs of establishing the Database, as well as the expenses of operating it. The company must pay:

- A fee for the costs of issuing and granting the licence[14];
- A yearly fee equivalent to the costs of the Monitoring Committee, the Data Protection Commission and the Scientific Ethics Committee;
- The costs of informing the Icelandic public and dealing with requests for information[15];
- The costs of processing data for entry onto the database[16];
- The costs of computer hardware and software;
- And may make additional payments to the Treasury as agreed with the Minister, which shall be devoted to promoting the health service, research and development.[17]

One of the most contentious unresolved issues are the regulations that determine the details about the operation of the database. These are still in the process of being drafted by the Department of Justice and will direct the supervision of the database. The legislation provides for three different committees to oversee the running of the database.

- The role of the Monitoring Committee is to oversee the contracts between the medical bodies and deCODE regarding imputing personal information onto computer. The

[10] Icelandic Ministry of Health and Social Security *The Icelandic Act on a Health Sector Database and Council of Europe Conventions* February 1999 p6
[11] Council of Europe Steering Committee on Bioethics and Working Party on Biomedical Research *Report of the Hearing of Icelandic experts concerning the Law on a Health Sector Database.* Strasbourg, 4th May 1999 p25
[12] Art 10
[13] Art 5 (9)
[14] Art 4.
[15] Art 4, relating to Art. 8.
[16] Art. 5 (8)
[17] Art. 4 Act on a Health Sector Database 1998

Committee must look after the interest of the medical bodies and to help negotiate the conditions for access and the fee deCODE will have to pay.

- The Data Protection Authority will monitor the procedures that deCODE puts in place to record and handle personal data during the establishment of the database and its subsequent operation. It will also 'carry out further coding of personal identification, using the methods that the commission deems to ensure confidentiality best.'[18] The Data Protection Commission will oversee the procedure by which the different databases of tissue samples and genealogies can be interconnected.[19] If the Data Protection Commission can not be satisfied that the linking of the databases would maintain anonymity then it has the power to refuse to allow the connection.

- The Scientific Ethics Committee shall oversee the research questions that are processed on the database, along with information as to who is making the enquiry. The role of the Committee is to ensure that there is 'no scientific or ethical reason to prevent the study in question being carried out, or the questions being processed from the database.'[20]

If deCODE breaches the terms of the legislation, does not fulfil the conditions of the licence or becomes unable to operate the database then the licence can be revoked. If deCODE used the database for a purpose other than those stipulated in the legislation or in the regulations then it could lose its licence. A breach of confidentiality on behalf of the employees of deCODE could jeopardise the licence agreement or lead to a fine or imprisonment. This duty applies even when employees leave their employment.

3.1.5. Consent for inclusion in the database

Despite continuing criticism, the Icelandic government has chosen not to seek the consent of individuals before including their medical records on the Database. It will instead rely on an 'opt-out' process. The reasoning for this decision is as follows:

- Records would be anonymous and so would not represent a breach of privacy or require consent for their use;
- The database is commercially more viable if all Icelandic medical records are on it, and gaining consent from the whole population might prove to be too difficult and would therefore jeopardise the completeness of the database;
- People have had 6 months (which has now been extended to 9 months or longer) in which to opt-out. Parents are able to withdraw their children's records from the Database, but it is unclear whether information about deceased people can be withdrawn;
- Once a record has been added to the Database it cannot be removed. However, an individual can request that no further personal information will be entered onto the system.

While there has been much criticism of the decision not to seek consent, this has been an accepted research practice for epidemiological research in both the UK and internationally. An

[18] Art 7
[19] Art 10
[20] Art 12

extreme (and possibly outdated) example of this policy is found in the International Guidelines laid down by CIOMS and WHO[21]. These state that:

> 'Epidemiological studies that involve the examination of documents, such as medical records, or of anonymous 'leftover' samples of blood, urine, saliva or tissue may be conducted without the consent of the individuals concerned, as long as their right to confidentiality is assured by the study methods.'[22]

The general view in the United Kingdom is that personal information in such studies should be anonymous, and if the research does not harm the individual and a research ethics committee has given approval, then consent is not required. Furthermore, the Royal College of Physicians [23] are divided as to whether research ethics approval is needed at all and the NHS Executive also believe that medical records can be used without consent. [24]

However, the recent ruling in the courts, *R v. Dept. of Health ex parte Source Informatics*[25], suggests that this practice is now unlawful. It has therefore brought into question the nature of established practice regarding the use of personal information in medical research in the United Kingdom.

3.1.6. The design of the Database - making the information anonymous

Much concern has focused on how to make the database anonymous to ensure privacy, while at the same time allowing new data to be added to existing records on the database. In order to ensure that the data is anonymous information will pass through three layers of coding.

- The first encryption of the personal identifiers will be irreversible. This will be carried out by medical professionals based in hospitals or doctor's surgeries. They will be responsible for putting the data onto the database, will employ extra staff to do this, and are bound by professional codes of confidentiality. The type of information that will be taken from the medical records is still undecided. The medical information will be encoded but there will be a public key for encryption and a private key for decryption of this information. Unlike the personal identifiers it will only be encrypted once before entering the database.
- The second encryption of personal identifiers would be carried out by the Data Protection Commission.[26] The Data Protection Commission, a government body, can neither read the original personal identifiers or the original medical information.

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[21] Council for International Organisation of Medical Services (CIOMS) in collaboration with the World Health Organisation 1993 *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Geneva.

[22] Council for International Organisation of Medical Services (CIOMS) in collaboration with the World Health Organisation 1993 *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Geneva.p28

[23] Royal College of Physicians Committee on Ethical Issues in Medicine, 'Research based on archived information and samples' *Journal of the Royal College of Physicians of London* Vol. 33 No. 3 May/June 1999, 264.

[24] NHS Executive *The Protection and Use of Patient Information* HSG (96)18 1996

[25] Lloyds Law Reports Medical. August 1999 264.

[26] Art 7

- The data then goes into the central Database where the personal identifier will be encrypted for a third time with a secret key held by deCODE Genetics. The intention is that deCODE Genetics when using the database will only be able to access encrypted information and will never have direct access to medical records.

The Data Protection Commission will be responsible for overseeing the linking of the Health Sector Database to other databases. deCODE want to link the Database with the Icelandic genealogies that are in the public domain, and existing sample collections that the company has collected. Exactly how this will be done to prevent the joining of personal identifiers is still to be worked out. The concern is that in a small country such as Iceland individuals are more recognisable than in larger communities and that the joining of different databases would enable individuals to be identified. It is also recognised that computer systems are fallible and that security cannot always be guaranteed. One measure designed to minimise this risk is that it will not be possible to extract information from the Database of groups smaller than 10 individuals.

3.1.7. The use of the Database and access by third parties

The exact procedures that will be put in place for access to the database are still not finalised. They will be the subject of regulations that are in the process of being drawn up. The Healthcare Sector Database Act requires that all research questions put to the database must be approved by a Science Ethics Committee, which applies equally to deCODE Genetics as well as other parties.

- While deCODE Genetics has the right to charge third parties for use, the company does not have the right to exclude and could find that its competitors would have to be given access to the database.[27]
- The Ministry of Health and the Director General of Health will always be entitled to statistical data from the Health Sector Database free of charge.
- In term of the research undertaken, the Scientific Ethics Committee will assess the scientific studies and questions put to the database, and whether, for example, insurance companies could commission research questions. However this is still undecided.
- It is not clear whether researchers based in Iceland would have to pay for access to the database or if deCODE will allow them access free of charge but subject to ethical approval.
- It is envisaged that a limitation will also be placed on the number of records that can be accessed at any one time.

3.1.8. The organisation of deCODE's current work on functional genomics

As outlined above, deCODE has already established research programmes aimed at identifying genes associated with common diseases, well before the IHD database will be created. These programmes now operate within the organisational framework established by

[27] Interview with David Thor Bjorgvinsson, Chairman of the Monitoring Committee on 6th July 1999.

the Act on a Health Sector Database, in particular the Data Protection Commission and the Scientific Ethics Committee.
All proposals for research are initially discussed by the Ethics Committee. Once approved, research first involves the collection of samples from patients affected by particular diseases. Lists of patients are initially generated from hospitals and clinics. These lists are then submitted to the Data Protection Commission who remove all personal identifiers apart from the social security number. These are then encrypted and the list is then given to deCODE in a form in which it is not possible to identify individuals directly. The list is then fed into the encrypted version of the genealogical database so that family pedigrees can be constructed. This is achieved by the fact that the code on the list corresponding with that used in the genealogical database.

Once extended family groups of interest have been identified anonymously, an encrypted list of participants for study is generated. This is then returned to the Data Protection Commission who decrypt the participant list and pedigree files. This is then used to generate the names and addresses of potential participants, and this list is then sent to deCODE's clinical collaborators. These doctors then visit patients in their homes to take a blood sample for genetic analysis. Samples and associated data are then re-encrypted by the Data Protection Commission and passed on to deCODE. Genotyping on the samples in then carried out by the company as a means of identifying disease associated genes.

If this system works as planned, the company can use it to identify members of extended family groups suffering from particular diseases, but without having either direct contact with the patients or finding out their personal details (name etc.). Similarly, the clinicians involved have no access to the genotypes of patients. The Data Protection Commission in effect provides a 'Chinese wall' through which information and samples pass in a way that provides some degree of confidentiality.

Clinical collaborators are funded by deCODE to collect these samples. By March 1999 the total funding of collaborating clinical departments and hospitals by deCODE was in excess of the basic funding of all medical research in Iceland provided by RANNIS, the country's main funding agency.[28] According to the company the bulk of this money was unrestricted. The company has also promised in the past to share revenues that flow from future corporate deals on specific projects with its collaborators.[29]

Samples may also be collected from Iceland's large tissue bank, which contain specimens from all autopsies and biopsies since 1915.[30] The country's medical record also contain historical data covering this 75 year period, and include information on the major illness suffered by its citizens.

[28] deCODE Genetics (1999). The Planned Healthcare Database in Iceland. Questions and Answers. deCODE genetics, Reykjavik.
[29] Moore, S.D. (1997) Missing Link. The Wall Street Journal Europe, July 3rd 1997.
[30] Moran, N. (1998) Iceland is Prime Territory for New Genomics Company to Study Isolated Population. BioWorld International 2(18) April 30th, 1998.

Already the company has successfully used this strategy to identify a gene responsible for a degenerative neurological condition, familial essential tremor, and a gene involved in an inherited form of endometriosis.

3.1.9. How might the Icelandic Health Sector Database be used for genetic research?

There is no clear information in the public domain about how the Database will be used for genetic research and many details of its potential use are still to be worked out. However, it seems likely that the Database will be used to identify patients and their relatives who suffer from particular conditions or adverse responses to drugs. Samples will then be collected in a manner that ensures confidentiality using the system outlined above. This will allow the company to hunt for genetic associations with common diseases across the whole population in a manner which enables linkage analysis and association studies to be undertaken.

3.2. UK genetics research using large biological sample collections

This section will briefly describe examples of existing and planned UK research projects involving the use of large biological sample collections, including the work of the biotechnology company, Oxagen, and a major national initiative being considered by the MRC and the Wellcome Trust.

At present there is no project in the UK which is equivalent to the Icelandic situation, as research is generally local to particular sample collections, is mainly based on group or family studies and does not involve access to electronic medical records. The level of commercial involvement is unknown, but already two UK companies have been established explicitly to work in this area (see Table 2). The examples described below have therefore been chosen to illustrate the type of research being undertaken and the issues raised, and are not intended to provide a comprehensive picture of research in the UK.

3.2.1. Initiatives under consideration by the MRC and Wellcome Trust

In 1998 the MRC received increased funding as a result of the government's Comprehensive Spending Review. In particular, it included in its bid a proposal to support national DNA collections as part of its Post-Genome Challenge. Several ideas were discussed, including the creation of a very large population study. The additional funding included £12 million earmarked for the creation of DNA collections[31]. The Council is currently planning how to support this type of research and is working closely with other funders of biomedical research, including the Wellcome Trust.

[31] Nature Medicine, (1998) 4 (12) p1346. MRC funds large-scale human genetic database.

At present no detailed information about the MRC's plans are in the public domain and many of the issues relating to the creation of large-scale sample collections are still being discussed. However, two main possibilities (which are not mutually exclusive), are under consideration. The first is the funding of a series of regional DNA banks, which could then be used as a resource by the biomedical research community as a whole. Samples would come from a range of studies funded on a project-by-project basis, and might also include samples from existing collections if appropriate consent had been obtained from donors. This would probably occur through support for 'private' collections by consortia or individual scientists, who would then be obliged to split samples and place part in the regional DNA bank. The banks would offer a genotyping service and access to data, but not to the samples themselves. At present there are no plans to link these banks in a systematic manner to medical information from NHS sources, but associated data characterising the samples will include medical information.

The second option involves the creation of a single very large new resource, the UK Population Biomedical Collection, in collaboration with other funders[32]. This proposal was first discussed at an expert workshop in May 1999 organised jointly by the Wellcome Trust and the MRC. It would be focused on genetic epidemiology and the Collection would enable prospective studies of genetic and environmental risk factors in diseases of later life. As a consequence of the need to analyse both genetic and environmental factors simultaneously, and the interaction between them, the proposed Collection would be very large, containing samples from up to 500,000 individuals[33]. Each of these would have to be linked to personal medical records. The prospective nature of the study would also span many years and require the ongoing collection of data from research subjects. The possibility of also using the Collection in a population survey of the immunological response to infectious diseases is also being discussed.

If such a large population collection were created, it would be a collaborative national effort. Genotyping would be done in centralised facilities and investigators would only have access to data, not to the samples themselves. All proposals for research would be peer reviewed. Companies would be able to access the data from the Collection, but only on a non-exclusive basis. However, the issues surrounding getting access to personal medical information and the prospective nature of the research have not been resolved, and no final decision about the creation of this resource is likely to be taken for some months. No details of the oversight of this proposal have been made public.

3.2.2. The North Cumbria Community Genetics Project

The North Cumbria Community Genetics Project (NCCGP) is a very long-term, collaboration between Westlakes Research Institute, Cumbria, and the University of Newcastle. It has been established with the aim of creating a resource that can be used in research looking at the interaction of genes, the environment and health. Cumbria is an attractive location for these type of studies as there is a stable population with relatively little genetic diversity.

[32] See People Power: population profiles and common diseases. Wellcome News, (1999) Q3, p18.
[33] (Ibid.)

The Project collects samples from the umbilical cord and the cord blood of babies born in the Whitehaven hospital. It initially planned to collect samples and medical data from 8,000 births over a five-year period and started work in 1996. As of October 1999 nearly 4,000 samples had been collected. In February 1999 the scope of the study was expanded and samples of maternal blood were also collected. This allows more powerful genetic analysis to be undertaken.

When the Project was first proposed, a series of public meetings were held and consultation took place with local communities and health professionals. The main issues raised during this process were confidentiality, the dangers of eugenics and how participation might affect people's access to life insurance. As a consequence, amendments were made to the research protocol and safeguards were adopted to ensure both the appropriate use of samples and data confidentiality. Assurances were also given that the community would be fully informed of progress on a regular basis through presentations to local organisations. The Project was finally launched after gaining approval from the West Cumbria Local Research Ethics Committee (LREC). In addition, NCCGP has established its own Ethics Advisory Group, composed of experts with experience of the ethics of genetic and epidemiological research. All new proposals have to receive prior approval from the LREC.

The Project is currently funded by British Nuclear Fuels, who operate the nuclear facility at Sellafield.[34] Whilst acknowledging that BNFL has an interest in studies of child health in the light of claims about a cluster of leukaemia around Sellafield, the Project stresses that 'BNFL have no role in the management of the Project and have not sought such a role.'[35]

Before samples are taken, women are asked for written informed consent and 85-95% of all expectant mothers agree to take part in the study. As a consequence, the collection represents the local, unselected population. Participants are also asked to complete a lifestyle questionnaire (workplace, smoking history, family health etc.) for both her partner and herself. There is little population movement in Cumbria and it is anticipated that the Project will follow the participants throughout their childhood and possibly into later life.

The Project operates on two sites, with the personal data stored in Newcastle in an encrypted form on a stand-alone computer with restricted access. The biological samples are processed and stored in Cumbria. A coding system links the mother's data to her child's sample and, to enhance confidentiality, the precise details of the samples are stored at Newcastle and are not available at Westlakes.

The Project, in consultation with its Ethics Advisory Group, has drawn up a 'Statement on Acceptable Research Uses of Collected Samples'[36]. This seeks to define the types of research that might be carried out with the collection. In particular, the Statement identifies three categories of study:

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[34] Westlakes Research Institute was established largely as a spin-out from BNFL

[35] Chase,D et al. (1998) The North Cumbria Community Genetics Project. Journal of Medical Genetics, Vol 35 (5), p413-416.

[36] (Ibid.)

'*(1) Studies that use anonymous samples to determine the frequency of alleles at specific loci or of polymorphism variants.* Subject to (3) below, there are likely to be few ethical difficulties with the use of NCCGP samples for such work …
(2) Studies that involve linkage to data on individual subjects. … Identification of individual people during the process and reporting of any such study will be done in such a way as to safeguard confidentiality.
(3) Studies that involve personality disorders, psychiatric disease, mild intellectual difficulties, and other sensitive areas. Such studies are particularly sensitive, and strong evidence of specific health benefit would need to be shown.'[37]

The consent form clearly states that research using the samples collected may involve reference to the health records of the mother and the baby. A further information leaflet also states that:

'In some studies the family doctor will be asked about the health records of a number of children. This is to help understand what the genetic variation mean. In these cases the family doctor will not be told of anyone's genetic study results.'[38]

It is also the policy of the Project that individual results will not normally be reported back to participants. However, it is clear that it will be possible for the researchers to identify individuals with particular genotypes:

'In rare and extreme circumstances when there may be an immediate major health benefit, the West Cumbria Local Research Ethics Committee would be asked to consider whether it is in the family's interest for an individual result to be disclosed.'[39]

However, the researchers involved in looking at personal medical records do not normally have access to information about a participant's genotype and the Project stresses that this would only be possible in extreme cases.

In order to develop its sample collection NCCGP seeks to establish collaborative research links with other organisations, including companies and academic groups. It has previously had interest from the pharmaceutical industry. However, this has not been translated into any formal collaboration, as companies were interested in owning the sample collection, and the sale of DNA and data is explicitly outside the remit of the Project.

As of October 1999, a series of eight academic collaborations had been established, including Projects with investigators in London and Cambridge. In some of these studies the North Cumbria collection is being used as an anonymous control group, whilst in others it is the focus of investigation in its own right. Research already completed, underway or approved to start includes studies of di George Syndrome, BRCA2, DNA repair genes and families with a high incidence of neural tube defects. In this latter case, this would involve trying to identify polymorphisms (SNPs) associated with an increased incidence of these defects.

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[37] (Ibid., p415)
[38] Further Information Leaflet (undated). p6. The North Cumbria Community Genetics Project, Cumbria.
[39] [39] Chase,D et al. (1998) The North Cumbria Community Genetics Project. Journal of Medical Genetics, Vol 35 (5), p415

3.2.3. Oxagen

Oxagen is a private biotechnology company based in Oxford established to investigate 'fundamental insights into the molecular biology of common human disease'. It was founded in 1997 as a spin-out from the Wellcome Trust Centre for Human Genetics at the University of Oxford. It also has very close links with the Nuffield Department of Clinical Medicine, the largest group of clinical researchers in the UK. Initial funding of £10.5 million was provided by a range of investors, including the Wellcome Trust. The company currently employs about 50 staff.

In collaboration with leading clinical research groups Oxagen is creating large, well-characterised sample collections from families with 'predispositions to specific diseases.' These collections are then used in conjunction with family pedigree information and clinical data to perform linkage analysis using high-throughput genotyping. The company also uses positional cloning, SNP analysis and epidemiology to build a picture of disease gene diversity. In the longer run it is interested in using information about disease related genes and associated polymorphisms to undertake detailed studies of pharmacogenetics and develop diagnostic markers to improve the targeting of therapy.

Oxagen has also raised the possibility of developing a large database of medical records, family pedigrees and genotypes as a tool for genetic studies of common diseases. However, it is not actively pursuing this option at present.

The company is interested in three broad areas: women's health, coronary artery disease, and inflammation and autoimmune diseases. Its programmes are spread throughout Europe and the US, and involve 31 collaborators in 22 centres. In women's health Oxagen recently signed a five-year collaboration with six European bone research groups to identify 'osteoporosis-related genes'. 3,000 osteoporosis sufferers and family members will be recruited by investigators from Oxford, London, Aberdeen, Southampton, Cambridge and the Netherlands. Milestone payments received from pharmaceutical companies developing drugs based on the research findings will be channelled back into research at each centre. So far Oxagen has committed £600,000 to the first two-year programme of collections in this area.

In its coronary artery disease (CAD) programme the company plans to collect samples from over 10,000 affected and unaffected family members. In is collaborating with Procardis, a European consortium of four research centres working on CAD.
Its research is carried out in the following manner. All of its clinical research is done in collaboration with academic investigators, many of whom have already been working with family sample collections for some time. The clinicians undertake all direct contact with participants and Oxagen never sees patients. Full consent is obtained, and research subjects are also told that a commercial company is involved and they are asked to disclaim any rights to future financial gain arising from the research. However, Oxagen stresses that it does not ask them to disclaim ownership of their sample and medical records. The ownership of samples therefore remains in the public domain. At anytime patients can withdraw samples from the study by asking the doctors involved. Furthermore, the company can't link samples

to the names of participants, as only coded materials and information is passed on by the doctors. In effect, the clinical collaborators provide a Chinese wall, which ensures confidentiality.

Consent is only given for a specific application/ study in a given disease area and the company can only use the sample in a tightly defined manner. The use of the complete collection is also governed by a research steering committee, which has a majority of academic members and representation from Oxagen and any corporate partner. At their discretion the steering committee can make samples available for other research studies. The only stipulation is that Oxagen has an exclusive license to commercially exploit the collection for a fixed period of time (usually 3-5 years). It is therefore asking for a 'commercial head start' and not a monopoly over the use of the collection.

Oxagen funds the process of collection and has agreed to share milestone and royalty payments from deals with large partners. This provides an incentive for participants who can then feel they are helping generate additional income for research and the development of services at the academic centre. Each participating institution has the property rights to the samples it collects and they pool their interests through the creation of a research consortium. All materials are returned to the academic centres at the end of the study. In terms of protecting its intellectual property Oxagen aim to patent polymorphisms with disease associations (but not the gene itself).

Every proposal for research has to receive prior approval from a research ethics committee (usually an MREC). In addition, patients do not get any feedback of the results of the research. This is for two reasons; firstly they are only involved in a research study and secondly, if they did receive feedback this could classify as a genetic test for insurance purposes. The main issues raised by MRECs have concerned the recruitment of family members. This has been handled by getting the patients to make initial contact with their relatives.

If a pre-existing collection was being proposed for study, the steering committee would take a view about the level of consent obtained and if it was possible to use the samples in a commercial study. Where possible clinicians recontact people to seek consent, although the view of MRECs is often that the original informed consent for a research study is enough. In general, the company feels that existing sample collections established for other purposes are of limited value.

Oxagen only makes use of fairly limited clinical information in its research. Permission to access medical records is included in the consent form, in line with standard Good Clinical Practice (GCP). The main concern is to validate the primary diagnosis and only relevant information is collected. No medical records are received by the company and the only information used by Oxagen is contained in a questionnaire completed by the clinical collaborators. The form is coded, so that no personal identifiers are present and the same is true of the samples and pedigree data. Information is therefore only stored in a coded form.

3.2.4. Other potential sources of large biological sample collections in the UK

There are a number of potential sources of large biological sample collections in the UK. The following list is not meant to be comprehensive, but gives some idea of the types of existing resources available.

a) Longitudinal studies of health status

These epidemiological research projects normally involve following cohorts or populations of people for fairly long periods of time. During the course of the study medical data, biological samples and other lifestyle information may be collected is order to examine the interaction of biological and social factors in determining health status.

The biggest of these studies is the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) which has been following 14,000 families originating in the Avon area since 1991. As part of the research a number of biological samples have been collected from participants. The ALSPAC project has received some industrial funding, but has not yet secured a collaboration with a biotechnology or pharmaceutical company to exploit its collection for genetics research.

Similar research projects which involve large-scale sample collection include the Whitehall II study, the European Prospective Study of Cancer and several national birth cohort studies.

b) Family sample collections

Several medical research charities have long established family-based sample collections, which have been established to facilitate research on specific diseases. These include fairly large collections held by the British Diabetic Association and the Arthritis Council.

c) Guthrie cards

Guthrie cards are the name given to the way in which the blood taken from newborn babies for genetic screening programmes has been traditionally stored. Many countries have used heel pricks to remove small amounts of blood from infants, for use in a simple biochemical test for PKU deficiency. This has been a practice in many parts of the NHS, although the extent to which these samples are retained varies from region to region. A survey of newborn screening laboratories in the US has revealed that these samples were being increasingly retained for possible future research purposes[40]. Little in known about the status of these samples in the UK.

[40] McEwen, JE. and Reilly, PR (1994) Stored Guthrie Cards as DNA "Banks" Am. J. Hum. Genet. 55, p196-200.

d) Other sources

A recent survey of biological sample collections in the US revealed a wide range of sources of collections, including pathology laboratories, the military, teaching hospitals, national research laboratories and various blood and tissue banks.[41] A similar pattern is likely to exist in the UK.

3.2.6. Other possible uses of large sample collections

There are a few non-medical DNA banks that have been established in the UK, most notably the Police National DNA Database. The bank was originally established as a forensic resource for helping identify criminals involved in serious offences, such as murder and rape. At the end of 1998 it contained about 350,000 samples from known suspects and 38,000 samples from the scenes of unsolved crimes. DNA fingerprinting technology enables samples taken at the scene of a crime or held in the database to be compared with a suspect's DNA. A positive match can then be used as evidence during prosecution.

The Criminal Justice and Public Order Act (1994) amended the original provisions to enable body samples to be taken for DNA analysis 'in broadly the same circumstances as fingerprints'. Non intimate samples (mouth swabs or hair samples) can currently be take without consent from any person convicted or suspected of a recordable offence.[42] Proposals to further increase the scope of DNA collection have recently been published.[43] If fully implemented they would enable the retention and use of DNA samples collected from volunteers during a criminal investigation, and the ability to use 'DNA samples … taken here against those from outside the jurisdiction …' (i.e. collections held in other EU states).

In recent years the Police Superintendents' Association has called for the creation of a national DNA bank with samples from every member of the population, but this would raise major civil liberties issues as well as costing over £1 billion to establish. As a consequence it is not official policy.

At present there are no proposals to use medical sample collections for criminal investigations using DNA fingerprinting. This would require the analysis of every sample in a collection and this would be prohibitively expensive. However, this situation might change in the long-term once cheap high-resolution genotyping with markers such as SNPs became widely available. In principle, the pattern of high-resolution markers carried by an individual might be able to act as a crude DNA fingerprint. Such information might in the future be collected routinely as part of medical research and could then be accessed by the Police. At present, this is a distant prospect.

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[41] Eiseman,E (1999) Stored Tissue Samples: An Inventory of Sources in the United States. RAND Critical Technologies Institute, Washington DC.
[42] Home Office (1999) Proposals for Revising Legislative Measures on Fingerprints, Footprints and DNA Samples. Home Office, London.
[43] (Ibid.)

4. The UK legal and policy framework governing genetic research using large biological sample collections and personal medical information

The following section will present a brief overview of the existing legal framework governing the following issues in relation to medical research in the UK:

- Ownership (patenting) of human tissues/ genes
- Consent of research subjects and use of data/ materials collected
- Confidentiality of medical information, privacy and data protection
- Third party access to materials and medical information

This review will provide the framework for the subsequent discussion of the issues raised by the use of biological sample collections and personal medical information. In particular, it will allow a judgement to be made about the adequacy of existing policies, practices, laws and regulations. Some key issues for social sciences research will then be suggested.

4.1. The legal framework: the law applying to medical research in the UK

There is no legislation in the United Kingdom that regulates research on human beings, although there is legislation that covers research on animals.[44] There have also been few cases that have been directly related to the conduct of research. This means that the law applying to medical research is largely dependent on the common law principles of consent and confidentiality developed for treatment, and various European Conventions and Directives. At an international level the European Convention on Biomedicine and Human Rights,[45] deals specifically with biomedical research. However this convention still has not been signed by the United Kingdom[46] and so while it is authoritative, it cannot as yet be considered to be a part of United Kingdom law until it is ratified.

Guidelines[47] issued by such institutions as the Royal College of Physicians of London, the Medical Research Council, and the Department of Health have a quasi-legal status as they set the standards that determine how medical research is carried out in the United Kingdom. If a case ever reached the courts, these guidelines would be considered when determining the

[44] *Animals (Scientific Procedures) Act* 1986.
[45]Convention for the Protection of Human Rights and the Dignity of the Human Being with regard to the Application of Biology and Medicine(Convention on Human Rights and Biomedicine) ETS No. 164
[46] Visit to the Council of Europe web site http://www.coe.fr/tablconv/164t.htm 21st September 1999.
[47] Royal College of Physicians *Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects* London: The Royal College of Physicians 3rd Edition 1996 and Department of Health *Local Health Research Committees* OHSG (91) 5. London: Department of Health 1991

lawfulness of research practice. In the past year the Medical Research Council,[48] the Royal College of Physicians of London[49], and the Royal College of Pathologists[50] have drawn up new guidelines in order to find ethical and legal solutions to the dilemmas that the use of biological material in research creates.

Medical research is regulated by Local Research Ethics Committees (LREC's), and Multi-centred Research Ethics Committees (MREC's). These Committees use the guidelines issued by the professional bodies to monitor research proposals and to make ethical decisions. The guidelines of the professional bodies draw on principles that have been set at an international level by the World Medical Associations Declaration of Helsinki and the COIMS/WHO Guidelines on Biomedical Research.[51] Essentially these guidelines require that research should only be carried out on an individual if informed consent has been obtained with approval from an independent ethics committee.

These bodies are comprised of people from different backgrounds and make decisions that can reflect local concerns and therefore may vary across the country. In assessing research proposals these committees have to balance the rights of individual research subjects against that of society's need for research, and this tension becomes particularly evident in assessing new research directions. The role of the research ethics committees is to determine ethical questions, their decisions do not have legal standing.

The following sections will discuss the law regarding the ownership of tissue samples and medical records, and the common law doctrines of consent and confidentiality. The purpose of this section is to show:

- The limitations of the common law
- How European law is placing new requirements on research practice
- How the ethical guidelines of professional bodies may differ from the law

4.2 Ownership

In DNA banking there are different things that can be owned and have rights attached to them. The legal rights vary depending upon the nature of the 'thing'. The lawfulness of the acquisition will determine the lawfulness of its subsequent use by another party. This section will explore

[48] Medical Research Council 1999 *Report of the Medical Research Council Working Group to develop Operational and Ethical guidelines for collections of human tissue and biological samples for use in research.* Third Working Draft.
[49] Royal College of Physicians Committee on Ethical Issues in Medicine, 'Research based on archived information and samples' *Journal of the Royal College of Physicians of London* Vol. 33 No. 3 May/June 1999.
[50] A statement from the College of American Pathologists, endorsed by the Royal College of Pathologists 'Recommended Policies for uses of Human Tissue in Research, Education and Quality Control' 1997.
[51] Council for International Organisation of Medical Services (CIOMS) in collaboration with the World Health Organisation *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* Geneva:1993

the ownership of the tissue sample, medical records, the DNA database, and the information that is derived from research.

4.2.1 Tissue Samples

The law has traditionally regarded that human tissue samples have no legal status. However, the development of new technologies and the increasing importance of biological samples in genetic research have given human tissue samples a new value and importance. The legal status of tissue has now become an issue for consideration, as it is a means of deciding who has rights over tissue samples, and how they can be used and under what circumstances. In this area the common law has not developed to accommodate the new uses of tissue samples and the ethical issues that are raised by this.

Tissue samples are parts of the human body that are removed by:

- 'The aspiration of bodily fluids (for example, blood) through a needle,
- By the scraping of cells from a surface (for example, skin or cervix),
- Surgical removal (such as organs or biopsies),
- Or collection by non-invasive procedure (e.g. semen).'[52]

A sample might be left over from an operation, collected as part of an autopsy, used for diagnosis, donated for research, kept in a tissue bank for further use in treatment or archived for research purposes. The way in which a sample is derived has implications for ownership and its subsequent use in research.

a) The Common Law

The common law position is that there are no property rights in the body except:

- In the cases of the theft of hair[53], urine [54] and blood[55] samples
- Where body parts have acquired different attributes 'by virtue of the application of skill, such as dissection or preservation techniques, for exhibition or teaching purposes.'[56]
- When relatives need to dispose of a body.

The recent case of *R v Kelly*[57], in which body parts were stolen by an artist, found that there could be property in a body part if 'work' and 'skill' has been expended on the body part. This decision has implications for the use of DNA samples derived from dead bodies as it suggests that if there has been the application of skill and work in isolating the DNA then the person or institution that does so gains a property right over the DNA sample. This is a more comprehensive right than the personal right of the individual to bodily integrity that is protected

[52] Office of Technology Assessment (1987) *New Developments in Biotechnology: Ownership of human Cells and tissues.* Washington DC.
[53] *Herbert* (1961) 25 J Criminal Law 163
[54] *Rv. Welsh* [1974] RTR 478
[55] *Rv Rothery* [1976] RTR 478
[56] Grubb A. "'I, Me, Mine': Bodies, Parts and Property" *Medical Law International* 1998 Vol.3 299, 307.
[57] [1998] 3 All ER 741

by the common law doctrine of consent. A property right entitles the owner to use or exploit the thing, to protect the thing against unauthorised use, and to allow transfer by gift or sale. This means once the DNA has been isolated from a sample it could be used without permission for research by an institution or a company. This in effect gives greater rights over the sample to the person or institution that has isolated the DNA, than the individual from which it was derived. It is not clear whether this case could also be applied to tissue from living individuals and the context of DNA banking. If it did, this would raise a number of ethical concerns about the protection of the interests of individuals, and whether it is appropriate that individuals have no rights over the use and control of excised tissue samples. This is of special concern because of the nature of the genetic information that can be derived from tissue samples. However, the court in *R v. Kelly* was not prepared to challenge the no property rule in the body, preferring to leave this to Parliament and the introduction of legislation.

b) Legislation

Legislation in Britain has adopted a property type approach allowing individuals to determine what happens to their tissue and organs after removal.

- The Human Organ Transplants Act 1989 allows donors to determine to whom organs will be donated and under what circumstances.
- The Human Fertilisation and Embryology Act 1990 requires that individuals must give explicit consent for subsequent use of their sperm and gametes, so that control over the body part and tissue is not restricted just to its removal but also to subsequent use and disposal.
- The Polkinghorne Report[58] recommended that explicit consent should be obtained from a mother when seeking permission to use a foetus in research.

One of the concerns of the adoption of a property approach, that is the turning of body parts into 'things', is that this would allow the sale of organs and human tissue.

- The Human Fertilisation and Embryology Authority allows payment for the donation of sperm and eggs of a nominal amount, that recognises the value of the donation but does not act as an incentive to donate.
- The Human Organ Transplants Act 1989 does not allow the sale of organs.
- Article 21 of the European Convention on Biomedicine and Human Rights[59] also prohibits financial gain from the human body and its parts.

c) Professional Guidelines

While the common law has adopted a non property approach to excised parts of the body, the recently established MRC Working Group on Collections of Human Tissue and Biological

[58] The Polkington Report (Review of the Guidance on the Research Use of Fetuses and Fetal Material (Cmnd 762 1989)

[59] Convention for the Protection of Human Rights and the Dignity of the Human Being with regard to the Application of Biology and Medicine(Convention on Human Rights and Biomedicine) ETS No. 164

Samples for Use in Research has taken a different view. It argues that 'tissue samples or collections of samples may be treated in law as property, and that legal and ethical advantages result from doing so.'[60]

The benefits of a property approach are that it would also allow an individual some control over a tissue sample once it is removed from the body,[61] as a property approach embodies the idea of rights and duties between parties; and it would enable a researcher or institution to deal with samples in a lawful manner. On transference a researcher or an institute would have property rights that would mean that it would be able to regulate the use and access to tissue collections and DNA Banks to third parties.

Property can be transferred in a number of ways, by sale, abandonment and as a gift. The sale of the human body or parts is not seen as desirable for ethical and social reasons and therefore much of the discussion has focused on transfer as a gift or by donation and abandonment.

d) Gift or Donation

To characterise the transfer of ownership in a tissue sample as a gift is to acknowledge the altruistic nature of research but also to allow the donor to specify how the sample may be used. The right to specify how the sample would be used would only exist before transference of the ownership interests, possibly at the time when consent was given.

Once a tissue sample was transferred as a gift or donation then the individual would also give up any rights to a share of the profits derived from a commercial application dependent on the sample.

However this analysis does not adequately deal with situations where informed consent has not always been obtained, for instance in the case of archived samples where the nature of consent is not always known, or with tissues derived from surgical waste.

e) Abandonment

The view recommended by a Nuffield Council report was that tissues derived as surplus waste from operations or diagnosis or in tissue archives could be seen to have been 'abandoned' in legal terms. This would mean that having gained consent for the initial operation, then it would **not** be necessary to gain further consent to research work carried out on the tissue, as the individual would be seen to have abandoned their interest in the tissue.

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[60] Medical Research Council 1999 *Report of the Medical Research Council Working Group to develop Operational and Ethical guidelines for collections of human tissue and biological samples for use in research.* Third Working Draft.

[61] See discussion in Matthews P., 'A Man of Property' *Medical Law Review* [1995] 3 231-274

This argument was raised in the John Moore case[62] where a removed diseased spleen was used to develop a cell line, the MO line, which became the basis of a patent application. Although John Moore had consented to removal of the spleen, he was not informed of the subsequent research or the patent application. On appeal to the Californian Supreme Court, it was found that John Moore did not have any property rights in his spleen. He therefore could not pursue a claim in conversion and an interest in what happened to his tissues after removal, but had to rely on a breach of the physicians duty of care. The problem with this analysis is that once consent for removal is given, an individual whose tissue is used in a way that she does not agree with, will have no basis to control that use against third parties such as a pharmaceutical company.

However it does not follow that because consent was given for the operation that it can automatically be assumed that the individual has also given up their rights to the tissue. In the Australian case of *Moorehouse v Angus and Robertson* [63] it was held that there must be a clear and unequivocal intention to abandon. The giving of consent to the operation is agreeing to the removal of the tissue, it cannot be implied that this includes an intention to abandon the rights in the tissue for whatever use the doctor may decide.

This approach would mean that tissue samples that are already held in archives could be used in research and samples that are collected through routine operations could continue to be used in research. This is problematic in considering the ethical issues and respect for individual dignity but is expedient in terms of the practical considerations of having to re-contacting individuals after operations.

4.2.2 Medical Records

These are generally regarded as being 'owned' by the NHS in the United Kingdom. This ownership interest is more that of a custodian, as patients may have access to their medical records. The personal information contained in them is protected by common law principles of confidentiality, professional codes of conduct, the Data Protection Act 1999, and possibly the Human Rights Act 1999 (see below).

4.2.3 The DNA Bank

Transference of tissue samples by way of a gift or donation raises questions about to whom the transfer is made. Is it the researcher or the institution that provides the funding for the research? Who then is responsible for the maintenance and management of access to the collection?

The MRC's position is that the funding body retains ownership of the collection (and can be shared ownership when there are a number of funding bodies) while the researcher is the

[62] *Moore v Regents of the University of California* (1990) 793 P 2d 479
[63] [1981] 1 NSWLR 700

custodian of the collection.[64] The custodian has the responsibility of control over the access to the collection and ensuring that standards of confidentiality are maintained. Funding bodies need to determine the purpose of the collection and if it is available to both commercial ventures and academic researchers on an equal footing. This is an ethical issue rather than a legal one.

The way in which DNA banks are characterised also affects ownership. If DNA banks are material to be owned, then common law principles are inadequate and there is no legislation that regulates their use and control. If DNA banks are seen as banks of information, then the Data Protection Act 1998 applies to collections of information that are held in computer or paper form, and legislative principles of consent and confidentiality apply.

4.2.4. Genetic Information

The whole purpose of DNA banks is to create information. Information is derived from tissue samples and the data that is associated with it can be derived from medical records and family histories. Not all information can be owned and the law prescribes strict categories for intellectual property rights. However the general principle in society is if you create some thing, then you are entitle to ownership of it in some form.

Essentially many of the agreements about ownership of research results and access to biological material and information are determined by multi-party private contracts and are not regulated by legislation. The general practice is that information belongs to the researcher or team that creates it and the individual who may have been a subject of the research has no legal entitlements to that research. Research is then protected under Intellectual Property regimes such as copyright or patent law.

4.2.5. Patents

The Intellectual Property right of a patent protects the use of an idea inherent in an invention, or 'the set of instructions which inventively solves a particular technical problem.'[65] It gives the owner the rights to sue for the wrongful use of the patent, the right to assign or license the patent to others, and to exploit the full commercial potential of the patent[66] for a period of twenty years.[67] The biological material that was the basis for the invention is not protected by the patent.

In order for the invention to be patented, it must fulfil the legal requirements of novelty, obviousness and utility. In addition to such criteria, an invention must not fall under the

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[64] Medical Research Council 1999 *Report of the Medical Research Council Working Group to develop Operational and Ethical guidelines for collections of human tissue and biological samples for use in research.* Third Working Draft. Para4.1

[65] Committee on Legal Affairs and Citizen's Rights *Report on the proposal for a Parliament and Council Directive on the Legal Protection of Biotechnological Inventions.* 25 June 1997 PE 218.021/fin, 33.

[66] see generally WR Cornish, *Intellectual Property* (3rd edn 1996)

[67] this is only 17 years under the USA Patent system 35 USC s.154 [1988].

statutory exclusions, it must not be a discovery, an animal variety, or an invention that is immoral, or contrary to 'ordre public'.[68]

Inventions based on human genetic information do not sit easily within this framework, and many have been challenged under the obviousness requirement, the prohibition on patenting discoveries, and as being contrary to 'ordre public'.[69]

Patent law has become one of the main legal strategies that are used to protect interests in inventions based on human genetic material. Since the early eighties, there have been 15,000 patents filed in the field of biotechnology by the European Patent Office, of which 4,000 were for genetic engineering in general, and half of these were for DNA sequences isolated from human genetic material.[70] The figure for patents that have been granted is less, as Thomas and Burke calculate that from 1981 to 1995, 1,175 human DNA sequence patents were granted worldwide.[71] There has been considerable controversy as to whether there should be patents granted over inventions based on human genetic material. [72]

Ownership in patent law does not require a consideration of the interests of a donor of biological material but is centred on the competing interests of the owner (which is usually the employer) and the inventor. The only case where an individual has sued for a share of the profits derived from a patent was the case of John Moore. On appeal to the California Supreme Court it was found that John Moore did not have a right to some of the profits of the patent over his cell line. This case lead to discussion of whether the human source should be protected from use of their genetic information.

The European Directive on the Legal Protection of Biotechnological Inventions[73] came into effect in July 1998. In the Recitals of the Directive there is the statement that if an invention is based on biological material derived from a human source, that person must have 'had an opportunity of expressing free and informed consent' before a patent is granted.[74] It will depend on the nation states as to how and if the intent of the Recital is manifest in national legislation. As it is only a part of the Recitals and not an Article of the Directive, it could be ignored in national legislation.

A recent WHO report recommended that if there are profits from the commercialisation of a patent derived from an individual then some profits should be returned to the human source.

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[68] see European Patent Convention Articles 52 and 53. These exceptions are found in ss.1(2) and 1(3) of the Patents Act (UK) 1997

[69] For example HARVARD/*Oncomouse* T19/90 [1990] EPOR 501, HOWARD FLOREY/*Relaxin* [1995] EPOR 541

[70] U Schatz, 'Patentability of Genetic Engineering Inventions in European Patent Office Practice' [1998] 28 IIC 2. These figures are in contrast to those stated by L Gruszow, in 'Types of invention in the field of genetic engineering, arising in the practice of the European Patent Office' in S Sterckx, (ed) *Biotechnology, Patents and Morality*, (Ashgate, Aldershot 1977) 149-158 who says that there were 12,500 patents granted for biotechnological inventions in general and 2,400 that relate to genetic engineering.

[71] SM Thomas & JF Burke. *Human Genome Patents; An Analysis of Ownership*. Intellectual Property Institute 1996

[72] For example HOWARD FLOREY/*Relaxin* [1995] EPOR 541

[73] Directive 98/44/EC of 6th July 1998, OLJ 213, 30.07.98, PP 13-21

[74] Recital 26 Directive 98/44/EC of 6th July 1998, OLJ 213, 30.07.98, 13-21, 15

In contrast Article 22 of the European Directive on Biomedicine and Human Rights prohibits financial gain from the human body and its parts.

4.2.6. Summary of the law on Ownership

The common law does not recognise any property rights in the body, so no one can own a tissue sample unless it is hair, urine or blood that has been stolen, or skill or work has been exercised over it. Legislation has taken a property type approach allowing individuals to control subsequent use of their organ or tissue.

4.3. Consent

4.3.1 Common law principles

The common law principle of consent in the UK protects an individual's bodily integrity against intentional touching or physical intervention. It will also allow a claim in negligence if it can be demonstrated that a doctor has not disclosed to the individual the material risks of the physical intervention. It does not protect the individual's interests if there is a secondary use of tissue.

a) Battery and Assault

The legality of the physical removal of a tissue sample and the interference with an individual's autonomy or bodily integrity will depend upon whether valid consent has been obtained from the patient. The legal principle of consent in the common law establishes that 'any intentional touching of a person is unlawful and amounts to the tort of battery unless it is justified by consent or other lawful authority.'[75]

In order for the intentional touching of a doctor to be immune from criminal prosecution, consent must be obtained from the individual before the procedure. An individual has the right to withdraw their consent at any time, and if a doctor continues to treat a patient this will be considered unlawful. 'This means that whenever the doctor engages in any new or additional therapeutic intervention, not covered by the previous consent, there arises a fresh duty to obtain consent and, thus to inform before the proceeding.'[76]

The exceptions to the requirement of consent are in emergency situations where a doctor may be forced out of necessity to act to save someone's life, and when a person may not be able to give consent because of a mental disability or mental illness.[77]

[75] Kennedy I. & Grubb A., *Principles of Medical Law* (Oxford University Press) 1998 Para3.02
[76] Kennedy I. & Grubb A., *Principles of Medical Law* (Oxford University Press) 1998 Para3.107

[77] section 63 of the Mental Health Act 1983 limits this to the treatment of the illness itself, while the case of *Re F* (a mental patient : sterilisation) [1990] stipulates this must be reasonably necessary and in the patient's best interests.

The common law is clear that consent must be given for the physical removal of tissue from an individual and without consent there is a violation of bodily integrity. It is less clear whether the consent for removal is vitiated if the subsequent use of the tissue is different from that which the individual agreed to when giving consent to its removal. For example, if a person consents to the removal of a blood sample for testing purposes and another test is then carried out on the blood sample, is this a violation of the individual's bodily integrity?

The common law position as established by the case of *Chatterton and Gerson*, [78] is that if the individual has been advised in broad terms as to the nature of the procedure to be performed, for example testing, then the fact that another test is carried out does not vitiate the consent that was given for its removal, as the physical removal of the blood through the syringe was done with consent. The USA decision of *Hecht v. Kaplan*[79] in the New York Supreme Court addressed this point specifically and found that the carrying out of a second test on the blood sample came within the original consent to remove the blood sample. These cases applied to situations were the secondary testing was for an individual's benefit, so that in broad terms the nature of the procedure was not considerably different to what the individual had consented to when the sample was removed.

However it could be argued that without specific knowledge that the second test was being carried out, the individual may think that consent has been given for a 'materially different procedure'.[80] This would depend on whether the court decided that the purpose for which the tissue was withdrawn was material to the giving of consent for taking of the blood sample.

It could be argued that if a doctor takes a sample for testing purposes and also for research purpose at the same time, without informing the individual at the time of the removal of the sample of the research, then this would be a breach of the consent to the removal of the sample. However if research was carried out at a later date after the removal of the sample, then it would be difficult to argue that a battery or assault had been committed retrospectively.

b) Negligence

A doctor has a duty of care to disclose to a patient the material risks associated with a medical procedure prior to acting, to ensure that proper consent has been given for those acts. A doctor should inform the patient of that which doctors as a profession think it appropriate for the patient to know.[81] This means that in the case of medical treatment a doctor has the discretion to withhold information from a patient out of concern for the patient's health. However a court may decide that information is so necessary for the patient to make a decision to consent to the treatment or not, that a doctor who fails to provide it would be in breach of his legal duty to his patient.[82]

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[78] [1981] 1 All ER 257
[79] 221 A.D.2d 100 (1997) and see also *Doe v. Dyre-Goode* 566 A 2d 889 (1989)
[80] Grubb A., & Pearl D., 'Blood Testing, AIDS and DNA Profiling' *Law and Policy* (1990) 8.
[81] para3.111 Kennedy I. & Grubb A., *Principles of Medical Law* (Oxford University Press) 1998
[82] *Sidaway v. Bethlem Royal Hospital* [1985] AC 871 HL

It is arguable that a doctor may breach their duty of care to the patient if they do not inform the patient that a test is to be carried out, especially if there are medical, social and emotional implications of knowing the results of a genetic test. It is unlikely that the physical removal of a DNA sample, through a blood sample for example, would result in a risk of misadventure or injury that the duty of negligence has been developed to cover. 'It is far from clear, therefore, that doctors owe their patients a duty of care to obtain each patient's specific consent to research or other uses of tissue, over and above consent to the original act of withdrawal.'[83]

4.3.2 UK Legislation

The legislature has imposed higher standards of consent for the removal of tissue from living persons than is required in the common law.

The Human Organ Transplants Act 1989 requires that the donor actually understands the nature of the medical procedure and the risks[84] rather than the common law requirement that people just need to be competent to understand, not that they actually understand what they are consenting to.

Under the Human Fertilisation and Embryology Act 1990 the donors of gametes and embryos must explicitly consent to the use of such tissue, and can impose conditions on use and may vary or withdraw any consent given.

The Human Tissue Act 1961 allows donated samples to be used for medical education and research, and requires that explicit consent is given before removal and use.

There is no legislation that applies specifically to the establishment of DNA banks and the storage and use of tissue samples.

4.3.3 European law

The Convention on Biomedicine and Human Rights requires informed consent for research and provides clear guidelines as to secondary use of tissue samples and information. Article 22 states 'when in the course of an intervention any part of the body is removed, it may be stored and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate information and consent procedures.' The implication is that if a tissue sample were used for a secondary purpose such as research, then the individual would have to be asked for their consent to this new use of their tissue sample. It would not be enough to rely on the fact that consent had been given for its removal from the body. If consent were not given for the secondary use, storage and usage of a sample for a purpose other than the original would be unlawful.

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[83] Magnusson R.S., in 'Confidentiality and Consent in Medical Research: Some Recurrent, Unresolved Legal Issues Faced by IECS' *Sydney Law Review* 1995 Vol 17 : 549

[84] Regulation 3(2) (b) of the Human Organ Transplants (Unrelated Persons) Regulations 1989 (SI1989/2480)

However the United Kingdom has not yet signed the Convention and it is no force in the United Kingdom until it is signed and implemented into United Kingdom Law.

4.3.4 Professional Guidelines

The standard of informed consent required by the professional guidelines is higher than the consent required by the common law.

In medical research informed consent must be obtained from the individual. The Declaration of Helsinki requires that 'each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort that it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time.'[85]

The doctrine of informed consent focuses on the individual and the quality of the information she needs to know about the potential benefits and risks of a procedure before she can make an informed decision.

It is not clear whether informed consent is required for the collection of **new** information and tissue samples for as yet unforeseen research purposes. The professional bodies differ as to whether informed consent is needed for new research on **existing** tissue collections or medical records. This is an issue that is still in the process of being clarified.

a) New Collections

The difficulty is that advances in technology may mean that the type of research and experiments that will want to be carried out on a tissue collection may change over time.

Informed consent would only allow 'the collection to be used for a very clearly defined set of experiments, this could lead to many new collections of samples being made unnecessarily or significant additional expense in re-contacting participants to obtain new consent.'[86]

Broad consent to the further use of a sample for research purposes would allow unforeseen research to be carried out on a tissue collection in the future without the need to re-contact individuals. Broad consent is ethically problematic because individuals would not be able to control the uses of their samples in future research.

The Medical Research Council Working Group[87] see that a solution is to obtain informed consent at the time of the collection of the sample and that broad consent should be obtained

[85] World Medical Association *Declaration of Helsinki,* Recommendations guiding physicians in biomedical research involving human subjects. Adopted in 1964 and updated in October 1996. Para 9
[86] Medical Research Council 1999 *Report of the Medical Research Council Working Group to develop Operational and Ethical guidelines for collections of human tissue and biological samples for use in research.* Third Working Draft. Para2.5

for the future unforeseeable uses of the sample in research. This should not specify that research will be for a specific disease, and that individuals should not be given the option to specify the types of research that they would not like their samples to be used for.

b) Existing Tissue Collections

The lawfulness of secondary research on existing collections will depend on the nature of consent gained when the sample was collected. It is over this issue that a balancing of the need for research and the protection of individual rights is particularly evident. The professional bodies have different views as to whether consent is required for secondary use.

The Royal College of Physicians regard that the secondary use of tissue samples does not require the express consent of the individual. As long as the information is anonymous and individuals cannot be identified; there is no harm or hazard to the individual by the research; and that an appropriate Research Ethics Committee has approved the research, [88] there is no need to seek consent. The concerns of the College are that requiring consent may 'bring to a halt all research on existing, archived material'. 'To attempt to contact very large numbers of people, often long after the event in question, and seek consent, would be impractical and probably unethical, since it would certainly involve in some instances a considerable and unexpected intrusion into people's lives.'[89] This is very similar to the approach that has been used in epidemiological research, where the practice has been that consent need not be obtained for non-intrusive research as long as approval had been obtained form an ethics board.

The Medical Research Council Working Group's position is that for older collections, tissue samples should be regarded as abandoned and therefore are able to be used for new research purposes as long as ethics committee approval is obtained. 'Samples should be anonymised, and the Research Ethics Committee must approve the safeguards put in place to prevent identification of individuals.'[90]

Although the advice of the Advisory Committee on Genetic Testing is limited to genetic testing it's position is quite different. 'Except where the study is conducted in a truly anonymised fashion, the Advisory Committee on Genetic Testing believes that before any genetic test is carried out as part of medical research prior consent must have been obtained for each test. Genetic testing should not be added to an existing research study without consent being sought.' [91] The Advice goes on to say that there may be some cases where new tests may be

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[87] Ibid

[88] Royal College of Physicians Committee on Ethical Issues in Medicine, 'Research based on archived information and samples' *Journal of the Royal College of Physicians of London* Vol. 33 No. 3 May/June 1999, 264.

[89] Royal College of Physicians Committee on Ethical Issues in Medicine, 'Research based on archived information and samples' *Journal of the Royal College of Physicians of London* Vol. 33 No. 3 May/June 1999, 264.

[90] Medical Research Council 1999 *Report of the Medical Research Council Working Group to develop Operational and Ethical guidelines for collections of human tissue and biological samples for use in research.* Third Working Draft. Para5.2

[91] Advisory Committee on Genetic Testing *Advice to Research Ethics Committees* October 1998, 7.

encompassed in the original consent. However if 'new tests are associated with other diseases and disorders which were not discussed with the participants, then a REC should conclude that both consent should be sought afresh and a new ethical review carried out.'[92] Also it 'is not ethically acceptable or (sic) participants to be asked to 'consent' in an non-specific manner to the carrying out of any and all gene tests.'[93] This suggests that if the new research were not included in the original consent then consent would have to be obtained again.

4.3.5 Summary of the law on Consent

The level of consent required for the use of tissue samples and personal information in medical research is still unclear. The common law protects the individual against an unauthorised taking of a sample, but does not allow the individual to control the subsequent use of it. In contrast, legislation allows individuals to control what happens to parts of their body and consent is required for subsequent use. European law requires that individuals must give consent to the taking of the sample, as well as any future uses, and reconsent must be obtained if the use was not specified in the original consent. It is still not clear whether the professional bodies regard that broad consent, rather than informed consent, should be obtained for new collections. This would be in accordance with the common law, but not necessarily European law. For existing collections views vary from not requiring consent for any new research, to the need for a reconsent for every new research question. Guidelines for research practice are still in the process of being developed and are complicated by the fact that the legislature has not taken a lead by implementing the Convention on Biomedicine and Human Rights into United Kingdom law.

4.4 Confidentiality

4.4.1 Common Law Principles

The duty of confidentiality in the common law applies to all types of information whether it is derived from DNA, tissue samples or medical records.

The common law duty of confidence requires that personal information that relates to the individual and is not public property or knowledge, which is disclosed in a confidential manner must not be given to a third party without the consent of the person concerned, or the person who is authorised to act on the patient's behalf .

Confidentiality will not be breached if:

- Explicit consent is given, either in writing or verbally, to the disclosure of the information.

[92] Ibid 7.
[93] Ibid 7

- The disclosure would be justified in the public interest, because someone or the public at large may be put in danger by the patient .[94]
- The disclosure of confidential information is required by statute e.g. Abortion Act 1967 and Public Health (Control of Diseases) Act 1984.
- The information is anonymous, and therefore no obligation of confidentiality arises. This has been put into doubt by the recent case of *R v. Dept. of Health ex parte Source Informatics* [95] (see below).

While this determines the situations in which information can be disclosed there is not a positive duty in the common law to disclose information, for instance to relatives effected by the results of testing.

The recently handed down case of *R v. Dept. of Health ex parte Source Informatics*[96] has brought into doubt the lawfulness of established medical research practice regarding the use of personal information in research. This means that many of the professional guidelines are out of date and unlawful in their advice. The case is very important in clarifying the law in this area and will go to appeal. The case established that:

- There is a duty of confidence for personal information given for the purposes of health care and treatment.
- The anonymisation of data (without aggregation) does not remove the duty of confidence towards patients who are the subject of the data.
- Personal information collected for the purposes of health care and treatment cannot be given to a third party for research purposes without the consent of the patients who are the subject of the data.

4.4.2 Legislation

The Data Protection Act 1998 will come into force over the next two years and supersedes the 1984 act of the same name. The new act now includes personal information held in paper filing systems as well as computers.

Consent must be obtained for the processing of data. Explicit consent must be obtained from an individual for the use of sensitive data relating to a person's physical or mental health, sexual life, racial or ethnic origin, religious beliefs, or (alleged) crimes[97] but not if it is done for medical purposes by a health professional.

The Act requires that personal data shall be processed fairly and lawfully; allows individuals to gain access to information held about them; and provides for a supervisory body to oversee and enforce the law.

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[94] *Wv Edgell* [1990] 1 All ER 835
[95] Lloyds Law Reports Medical. August 1999 264.
[96] Lloyds Law Reports Medical. August 1999 264.
[97] s. 2 Data Protection Act 1998

Personal data used for research purposes is exempted from the Act, if the purpose of the research 'is not measures or decisions targeted at particular individuals and it does not cause substantial distress or damage to a data subject.' [98] This does not include research that will be used to inform clinical decisions. This means that under the Act personal data used in this kind of research can be processed for purposes other than that for which it was originally obtained and be held indefinitely. Individuals do not have a right to be told how information is being processed if that data is anonymous.

This last point, while in accordance with research practice, is in conflict with the recent common law decision. Legislation tends to have greater authority than the common law, so it will be interesting to see how a higher court will deal with this. The new Human Rights Act 1999 will also have some bearing on privacy and the use of information.

4.4.3 Professional Guidelines

The case of *R v. Dept. of Health ex parte Source Informatics* [99] means that research practice will have to change. The professional guidelines were compiled before this decision.

The guidelines regard that the consent to treatment is seen as implied consent for this information to be given to other health care professionals. The Medical Research Council's opinion is that 'the transfer of confidential medical information between members of the medical profession is a necessary and accepted practice. The doctor is seldom the sole confidant, since effective care involves others, both medical and non-medical, technical and clerical, who provide services and manage the health care institutions.' [100] The Royal College of Physicians position is the same although it is narrower as 'it is expected that access will be limited to those to whom it is essential for the provision of healthcare.'[101] This is contrary to the common law doctrine of confidentiality.

Patient information can be used for research purposes without consent if it is anonymous and approval has been given by a research ethics committee. The acceptability of this view is changing within the professional bodies.

The NHS position is that NHS staff and sometimes staff of other agencies will use patient information, without consent, for research purposes 'in order to deliver, plan and manage services effectively.'[102]

The Royal College of Physicians consider that use of medical records in research is acceptable if the doctor's permission is obtained rather than the patient's. 'Research that involves no

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[98] Commentary to the Data Protection Act 1998 *Current Law Statutes* 1998 Vol 1 Chapters 1-31 Sweet and Maxwell.29-39

[99] Lloyds Law Reports Medical. August 1999 264.

[100] Medical Research Council *Responsibility in the Use of Personal Medical Information for Research – Principles and Guide to Practice* London : Medical Research Council 1994 p4

[101] The Royal College of Physicians *Research Involving Patients* London: Royal College of Physicians of London 1990.para 6.7

[102] NHS Executive *The Protection and Use of Patient Information* HSG (96)18 1996

more than the examination and analysis of a single medical record for each individual requires the consent of the responsible doctor or medical custodian. The patient's express consent need not be obtained.' [103] The Royal College of Physicians regard that non-intrusive research on medical information would not need consent.[104]

The decision in *R v. Dept. of Health ex parte Source Informatics*[105] found that personal information collected for the purposes of health care and treatment cannot be given to a third party for research purposes without the consent of the patients who are the subject of the data.

The professional guidelines attach a lot of weight to the fact that breaches of confidentiality may result in disciplinary action by the professional bodies. This is seen as a way of safeguarding individual interests. In research personal information must be handled only by health professionals or staff with an equivalent duty of confidentiality; all invitations to participate in research and re-contacting must be made through the individual's doctor; and Medical professionals are bound by codes of practice which means they are personally accountable for the use of patient information.

4.4.4. Anonymous Information

The professional bodies have regarded that there is no breach of confidentiality if information is made anonymous. This information could be used without the consent of the individual. However, the view that there 'is clearly no obligation of confidence owed with respect to information in a form which is not capable of identifying the patient'[106] is no longer true. The case of *R v. Dept. of Health ex parte Source Informatics*[107] establishes that the fact that data is anonymous does not remove the duty of confidence towards patients who are the subject of the data.

The law does not make distinctions between the level of identification of a sample that is possible and the implications that this may have for further use. Most professional guidelines also have not comprehensively explored the distinctions and its implications for use by medical professionals and safeguarding confidentiality. The belief that personal information can be used without consent has the potential to undermine public confidence in the medical profession and the relationship of trust that exists between a doctor and patient.

The use of anonymous data has been seen as a way to obviate the need for consent in research. The argument is that when data is anonymous and personal identifiers removed then

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[103] Medical Research Council *Responsibility in the Use of Personal Medical Information for Research – Principles and Guide to Practice* London :Medical Research Council 1994 p2

[104] Royal College of Physicians Committee on Ethical Issues in Medicine 'Research based on archived information and samples *Journal of the Royal College of Physicians of London* Vol.33 No.3 May/June 1999.

[105]. Lloyds Law Reports Medical. August 1999 264

[106] Kennedy I. & Grubb A., *Principles of Medical Law* Oxford University Press 1998 para 9.19

[107] Lloyds Law Reports Medical. August 1999 264.

the requirement for consent is removed and the individual loses the right to determine how personal information is used. This has now been called into question.

There is also some doubt whether DNA samples can ever be anonymous because of the its unique nature as an individual identifier. With the increase of databanks and the potential for information to be shared there is the possibility that individuals would be able to be identified. This could happen if one database had samples that included personal information while another had information that was unidentifiable.

4.4.5 Summary of the law on Confidentiality

Essentially the case of R v. Dept. of Health ex parte Source Informatics has changed the law regarding confidentiality in the United Kingdom and this could have an effect on research practice. While the Data Protection Act 1999 effectively endorses current medical research practice, the common law challenges it. The recent decision suggests that the following medical practices may be unlawful:

- Sharing of confidential medical information by the medical profession without consent.
- Use of medical records without consent.
- Use of anonymous information for research purposes without consent.

The law needs to be clarified in this area.

5. Overview of the ethical, social and legal issues raised in the UK by the use of biological sample collections and personal medical information in human genetic research

5.1. Conceptual issues raised by genetic associations with common diseases

The claims of recent work in genetics challenges previous assumptions about the underlying causes of many common diseases. Cancer is a good example of this. Twenty years ago only a handful of tumours were thought to be caused by inherited factors, but in the last decade a genetic model of the disease has started to dominate biomedical thinking. This new explanation is not based simply on the inheritance of cancer causing genes. Instead, the description of the underlying pathology is now couched in molecular terms (patterns of gene expression, activation of oncogenes etc). The role of environmental factors is still included in the model, but the emphasis has shifted to understanding how therapeutic interventions can be made at the molecular/ genetic level. This 'genetification' of pathology is occurring in the explanation of many other common conditions that had previously been seen as acquired as a result of environmental hazards and social factors. Far greater attention is now being paid to genetic predispositions and the inheritance of disease 'causing' genes. This shift is likely to have profound long-term implications for our understanding of health and illness, and the conduct of medicine.

One consequence of this new molecular pathology which flows from functional genomic studies is the segmentation of unitary disease categories into sub-groups, some of which are now thought to have a strong genetic element to them. For example, breast cancer, asthma and diabetes can all now be divided into different 'types', depending on their molecular biology. Whilst this may greatly help improve diagnosis and therapy, it further strengthens the shift towards genetic explanations of disease and raises questions about how medical practice will be developed around these new disease categories. For example, will routine genotyping become a part of clinical practice?

- What are the implications of the shift towards genetic explanations of common diseases for clinical practice and our understanding of health and illness?
- What are the philosophical and theoretical issues raised by the shift towards molecular pathology? How are new diseases categories 'socially constructed?
- What issues are raised by the ability to sub-type common diseases according to their molecular pathology?

5.2. The use of large biological sample collections by academia and industry

This paper has sketched out the main ways in which biological sample collections are likely to be used in genetic research in the immediate future. However, no attempt has been made either to quantify the scale of existing sample collections or to describe the use of such resources outside the field of functional genomics. A recent inventory of stored tissue samples in the United States[108] revealed that a conservative estimate of the number of samples held in the country was in excess of 282 million. Very large collections were held by the military, the National Institutes of Health (NIH), academic medical centres, pathology departments, new-born screening laboratories, forensic services, as well as a range of blood, cord and tissue banks. Furthermore, new samples are being collected in the US at the rate of 20 million a year and the NIH spent some $53 million in 1996 alone supporting extramural tissue repositories. Very little is known about the collection and storage of biological samples in the UK, but it is likely to be on similar scale.

The use of human biological samples in medical research in general and genetic research in particular, is pervasive. Well-known examples of where the analysis of tissue samples have played a key role in research include, making the link between the drug DES and cancer in women, and the link between smoking and lung cancer[109]. An understanding of the pathology of atherosclerosis, the role of HIV infection in AIDS, and the genetics basis of some colon cancers, has also depended on the use of biological samples.

- Where are large collections of biological samples held in the UK? How are they being used in research and for other purposes?
- What is the scale of the sample collection being created by industry for use in genetic research? Should there be a system of monitoring such large-scale private collections?
- What other types of genetic research outside the field of functional genomics and genetic epidemiology are making use of large sample collections? What new ethical, legal and social issues are being raised by this research?

5.3. The creation and use of biological sample collections in genetic research

5.3.1. Consent, and the creation and use of collections

The principle of consent is central to the process of creating and using biological samples in medical research. However, there is some debate as to whether the standard of fully informed consent can be met in every research situation. There are several reasons for this. Firstly, the

[108] Eiseman,E (1999) Stored Tissue Samples: An Inventory of Sources in the United States. RAND Critical Technologies Institute, Washington DC.
[109] Korn, D. (1999) Contribution of The Human Tissue Archive to the Advancement of Medical Knowledge and Public Health. National Bioethics Advisory Commission, Washington DC.

complexity of genetic research makes it difficult for participants fully to understand the nature of the study they are involved in. Secondly, at the time that new collections are created it is difficult to foresee all the potential research applications that the collection may be used for. Finally, in the case of existing collections it may be impractical to gain consent for new research uses from the donors of the samples. It can also be argued that different consents will be required for the physical taking of the sample, its use in a specific research study, its use by third parties, its subsequent use for other research purposes, and its use in a commercial application. Furthermore, each of these consents could have a different standard.

Other important issues are raised by the use of anonymous samples, which have previously been seen as relatively unproblematic. There is, as noted in Section 3, a need to be precise in the use of concepts and to distinguish between datasets being anonymous; encoded; or encrypted. The conceptual confusion here is such that this may in itself form a topic for research and investigation. However, even if the social arrangements for protecting confidentiality are clear, given the nature of genetic information, it may prove impossible to ensure that biological samples can be truly anonymous. This underlines the point that guarantees of confidentiality can never be absolute (doctors and researchers could be forced by court order to breach undertakings of confidentiality, for example) and raises the question of the degree to which it is reasonable to take steps to protect confidentiality. Ultimately, the question arises as to whether the principle underpinning existing practices is any longer tenable.

Within Western medicine consent has historically been seen as purely a matter for the individual receiving treatment or participating in research. However, genetic information about an individual is also shared with other family members and may have implications for communities. This potentially sets the rights of the individual against the interests of her family. Furthermore, if a family or specific community is to be the subject of research, then there is a case for saying that consent may be required at a group level. This requirement has now been recognised by the Human Genome Diversity Project, which supports the principle that community consent as well as individual consent should be sought for genetic research. It also requires that there must be express consent from the community before a patent is applied for and that all financial benefits derived from patenting should be returned to the community.[110]

- Is it possible to have informed consent given the complexity of genetic research?
- Is it ethically acceptable that broad consent for the use of tissue samples is the standard, which would mean that individuals would not need to be informed of every new type of research conducted on the collection?
- Does the nature of genetic research require that individuals should be able to express their approval for how their tissue samples might be used in each new type of study?
- Does the nature of consent have to be reconsidered in the light of genetic research? Do different forms of consent need to be obtained for different uses?
- For tissue that is gained as surgical waste or has been archived, is it ethical that these collections can be seen as abandoned by the individuals and therefore future research does not require consent?

[110] Greely H.T., 'The Control of Genetic Research: Involving the "Groups in Between" *Houston Law Review* 1997 33:1397

- For existing collections, is it sufficient that if information is anonymous and approval has been given by a research ethics committee, then consent is not needed for subsequent use?
- Is the ease or difficulty with which samples can be identified a relevant consideration? As the protection of confidentiality can never be totally guaranteed, should different standards apply to samples that are encoded (or encrypted) and to those that have been rendered anonymous? Or does this distinction make no difference as to the requirement of consent in research?
- Do the benefits of this type of research and the practical difficulties of re-consenting weigh against the interests of the individual?
- Is the concept of a gift, with conditions placed on its subsequent use, sufficient to protect individual dignity or does it just create an administrative nightmare? Is a property approach more likely to protect the interests of sample donors?
- Does the nature of genetic research, with its implications for other relatives, mean that consent should be considered as not just being relevant to the individual?
- Should this principle of community consent be recognised in the United Kingdom?

5.3.2. Privacy and data protection

Some of the most important concerns about the creation of the Icelandic database have centred on issues of privacy and data protection. In particular, there are doubts that the highly sensitive information about the genotypes of individuals can be kept fully confidential, especially when this information is related to other personal data, such as medical histories and family pedigrees. The use of coded samples in the UK raises similar questions, as in some situations it is not difficult to relate a sample to an individual, and it is only internal research policies and practices which prevent this from happening routinely. Where samples are truly unidentifiable (i.e. lacking any [coded] personal identifiers), this may be less of a concern, but as discussed earlier, it may become possible to attribute unknown DNA samples to individuals in the future.

Another set of concerns surrounds who has access to sample collections and databases of genetic information. deCODE plans to sell subscriptions to its database to pharmaceutical and insurance companies. Some people have questioned how access to information by these third parties should be controlled and if it should be on a different basis for academic researchers. The Icelandic Act has provision to regulate access and the use of the database, but many other genetics projects are not regulated by legislation of this kind. In the United Kingdom access by third parties to databases are determined by private agreements and the requirements of the Data Protection Act 1999. The conditions of each agreement regarding database access will vary and depend upon negotiations between parties. Oversight of these private contracts is only done by a court when things go wrong.

- Is it possible to integrate large databases of anonymous genetic, medical and family information in such a way that confidentiality can be maintained?
- Is the use of coded samples adequate to protect confidentiality?
- Will it be possible to attribute unidentified samples in the future?
- Should there be a right to genetic privacy?

- How should access to genetic databases by third parties be regulated? Should academics have different rights from companies?
- Are the provisions of the Data Protection Act adequate in the case of genetic information and biological sample collections?

5.3.3. Ownership

There are two common approaches to the ownership of tissue or parts of the body by the individual. The first is that no one has the right to control the usage of tissues or body parts once removed from the individual. The basis for this principle is that with the abolition of slavery, no one has the right to own someone else and this extends to the body. The extension of this is an emphasis on the sanctity of life and that no person should be treated as a commodity and no profit should be made from parts of the body. The second approach is that individuals should be able to determine what happens to excised parts of their body. One solution to this is to adopt a property approach, but property rights can give a right to transfer as well as allowing the right to alienate or sell parts of the body.

In terms of ownership of body parts by others, the philosophical underpinning of the law is that the exercise of skill and labour will be the basis for acquiring property rights in a 'thing'. Things can be tangibles such as tissue samples or intangibles such as information derived from isolated DNA. The recent case of *R v. Kelly* demonstrates the 'exercise of labour' approach and provides a justification for intellectual property rights in a patent.

Public policy with respect to the patenting of human genes appears to be in a state of confusion. A few years ago the UK government supported the EU Directive covering the patenting of human genes, but now appears to be arguing that gene sequence data should be public property. There are important questions which remain unanswered about the social acceptability of the private ownership of gene patents, and the impact this might have on scientific research, innovation and the costs of new medical technologies.

- Is it socially and ethically desirable for parts of the body to be commodified?
- Are there ethical differences between the use of genetic material derived from living donors and the dead?
- Does a property approach adequately encompass the ethical issues that surround human tissue or should new constructs be developed to deal with the use of the body and DNA in genetic research and biotechnology?
- Is the 'exercise of labour' approach an appropriate basis for gaining property rights in tissue and information that is derived from DNA?
- Is it ethically tenable that individuals may control the taking of tissue from their body, but can have no control over its subsequent use once it has been altered in some way?
- How does DNA fit into people's concept of themselves and their bodies?
- Is it ethically acceptable that individual tissue may be commercially exploited, but the individual does not have any basis for claiming a part of the profits?
- To what extent does the existing IPR regime surrounding the patenting of human genes adequately meet public policy objectives?

- What are the socio-economic consequences of the monopoly ownership of IPR covering human genes?

5.3.4. The commercial exploitation of biological sample collections

The field of human genetics research is marked by a very tight linkage between academia and industry. Many publicly funded research projects end up being commercially exploited and this is encouraged by public policy. However, where tissue samples are donated freely by participants in research studies there may be objections to the subsequent development of these resources for profit. This argument has formed the basis for maintaining a non-commercial blood donation service in the UK. If the 'gift relationship' was undermined, this might greatly reduce participation in public research.

Even if the potential economic benefits can be used to justify the commercial exploitation of public sample collections, there are still important issues concerning the basis on which this is done. The example of deCODE Genetics raises questions about the desirability of genetic resources being placed in the private sector and whether a single company should be give a monopoly over such information.

- To what extent does the close involvement of industry in the exploitation of biological sample collections compromise public support for genetic research?
- Should the private sector have the right to build large biological sample collections for genetic research or should such research always be carried out in public-private collaborations?
- Should commercial access to public sample collections and genetic information always be given on a non-exclusive basis?

5.4. The use of, and access to, personal medical information in genetic research

5.4.1. Consent and the use of personal health information

General issues concerning the nature of consent in medical research is dealt with in section 5.3.1 with respect to tissue samples and genetic information. However, some specific additional points concern the use of medical records.

At present medical records are often used in research without the consent of the individual. Ethically and more recently legally this has become problematic. The recently handed down case of *R v. Dept. of Health ex parte Source Informatics*[111] has brought into doubt the lawfulness of established medical research practice in this respect. The ruling means that many of the professional guidelines are out of date and misleading in their advice. It also has major

[111] Lloyds Law Reports Medical. August 1999 264.

implications for the commercial use of medical information and the creation of large databases. The case is very important in clarifying the law in this area and the appeal decision will be fundamental in shaping policy.

One of the important issues in the use of medical records is that they have been created to facilitate the treatment of the individual financed by the public purse. It is likely that this information will be used in collaborative research with privately funded companies, who will profit out of this information.

- Should medical information be routinely used in research without obtaining consent? Is the legitimacy of this practice affected by the use of anonymous medical information?
- Who can have access to medical records?
- On what basis should access be granted to third parties? Should access be different for publicly funded researchers and private companies?
- Can medical information be used for commercial gain or should it only be used for research?

5.4.2. Confidentiality, privacy and data protection

Many of the issues concerning the confidentiality of medical records are similar to those concerning tissue sample collections (described in 5.3.2. above). The creation of large electronic databases poses problems about security of information and how data should be protected against unauthorised use. Aspects of this are covered by the Data Protection Act. An important issue in this area concerns the way in which doctors can often be used as a 'Chinese wall' to protect the confidentiality of the research subject. For example, this was the policy chosen in Oxagen's research to ensure the company had no direct information about participants. However, it depends on the integrity of the doctors concerned, the nature of the professional guidelines, and the clear separation of medical records from genetic information (genotypes). The system of professional guidelines is backed up by the threat of professional disciplinary measures and the possibility of legal action.

- What are the professional codes of conduct that governs the handling of medical records during research? Are they adequate to protect the medical professionals, as well as the patients involved?
- Who is responsible for ensuring the confidentiality of personal information? Should there be additional oversight mechanisms?

5.5. The objectives and findings of research

The new information created by the integration of sample collections, personal medical records and genealogies relates to:

- The relationship between diseases and specific genes/ genetic variations in the sample population;

- The likelihood of individuals carrying the gene/ genetic variation developing the disease;
- The future health status of specific families, groups and populations;
- The way in which gene-environment interactions are involved in disease causation.

As a consequence this information is potentially very valuable to a large number of groups, including:

- Companies, who might patent the gene/ genetic variation and develop therapies and diagnostics using this information;
- Individuals and families carrying the gene/ genetic variant who may wish to know about their health prospects or want to seek advice and medical help;
- Doctors involved in the treatment of susceptible individuals and families;
- Third parties, such as insurers and employers, who may be affected economically by illness amongst their policy holders or employees;
- Government departments and health policy makers who are involved in the planning and development of health and social care services.

It is also important to realise that the generation of information about the genetic susceptibility of individuals is likely to far outstrip the development of therapies for these conditions. It is therefore possible to imagine a situation where large numbers of people can be diagnosed as being predisposed to a particular illness, but where this information is of no benefit to the individuals concerned. As a consequence, there are important public policy issues about the overall aims and benefits of the research, who should pay for the creation of sample collections/ databases, who should benefit economically from the research findings, and how the adverse consequences of this information can be minimised.

5.5.1. The social acceptability of genetic research

As illustrated by the case studies above, genetic research using large biological sample collections is potentially highly controversial. It is therefore important that the social benefits of research outweigh the risks to society and that the research objectives are socially and ethically acceptable. Without this, there is a danger that the legitimacy of all work on human genetics will be called into question. It is all the more so in cases where the topic of research is particularly sensitive, for example, in genetic studies of race, mental illness and behavioural disorders. As discussed above, in research projects based on the study of particular groups there may also be a need to develop new policies to ensure community consent, in addition to individual consent.

- How can public debate on the aims of genetic research be organised to ensure that participants are well informed and fully involved?
- What mechanisms, such as consultation exercises and citizens juries, are best suited to build social consensus and ensure that broad public concerns are reflected in official policy?
- How can the concept of community or group consent be put into practice in the UK?

5.5.2. The regulation, oversight and governance of research

In addition to ensuring that the aims of research are acceptable, it is also essential that the conduct of research commands broad public support. This requires a properly functioning system of regulation and research oversight, that operates according to clear ethical and legal principles, is transparent and involves a wide range of social groups.

The lack of primary legislation and comprehensive case law in the UK regulating medical research is surprising to the lay person. With the expansion of potentially sensitive and harmful genetic research, the case for more explicit legal regulation in strengthened. However, if the Convention on Biomedicine and Human Rights is incorporated into UK law this situation would clearly change significantly.

Whilst the established system of research ethics committees has worked well for conventional medical research, there may be a case to strengthen research oversight in the case of genetic studies. The greater involvement of lay people in the drafting of professional and official policies might also be seen to strengthen the oversight process. Furthermore, there needs to be clear social and legal sanctions to police the system of oversight and to ensure that research is undertaken at the highest ethical standards.

The regulation of sample collections and genetic databases held in the private sector is regulated in largely the same way as public research. However, in the light of the debate about deCODE Genetics there may be concerns that the commercial secrecy that surrounds the use of personal genetic information within private companies would make effective monitoring and oversight difficult. For example, relatively little is known about the increasingly common practice within drug company sponsored clinical trials of routinely collecting and storing samples for pharmacogenetics research.

- Is the existing legal framework adequate to regulate genetic research in the UK?
- Should the conduct of genetic research be formally regulated by legislation?
- What impact will the adoption of the Convention on Biomedicine and Human Rights have on the legal regulation of genetic research?
- How can research oversight be strengthened?
- Should there be a national bioethics committee that helps formulate policy and provides training for LRECS and MRECs?
- How might families and communities be involved in the oversight of research?
- What additional policies might research funders adopt to ensure that research is conducted to the highest ethical standards?

- Should there be additional safeguards to oversee the development and use of private/ company sample collections and genetic databases?

5.5.3. Commercial benefits of research findings

Many of the resources being used in genetic research have been developed using public funds and require high levels of public involvement and support (donation of samples etc). Whilst policy aims to encourage the commercial exploitation of publicly funded research there is also a recognition that this must be matched by a suitable social return, either in the form of local employment, the commercial funding of public research or licensing and royalty fees. In the case of research using donated samples, it is generally assumed that the individual donor is giving her tissue to further the collective good of the community, rather than the private profit of a company. However, as has been made clear in several of the case studies, in the future biotechnology and pharmaceutical companies are likely to commercially benefit from collections of tissues donated for research.

This raises important questions about who should pay for and who should gain from research involving biological samples. In addition, it creates the potential for conflicts of interest within the research community. For example, how should the custodian of a public sample collection behave if they wish to commercially exploit the collection for their own profit through the creation of a spin-off firm? The other objection to the heavy involvement of industry in human genetics research is that it can constrict academic freedom and open access to important research resources such as DNA banks. This has been a major worry for those sections of the Icelandic research community not associated with deCODE.

- On what basis should large sample collections, which may yield significant commercial benefits to industry be established? Should public-private consortia be created?
- How should these collections be financed and how should the financial benefits arising from them be shared?
- How should the commercial exploitation of publicly funded sample collections be governed to avoid conflicts of interest and to protect academic freedom?

5.5.4. Feedback of information to individual participants

Genetic research raises a number of issues about the disclosure of information derived from an individual's tissue sample. It would be a breach of confidentiality if a doctor or researcher did disclose the results of a test to other family members. Although, this may be legally correct, it raises difficult ethical questions, as the investigator could have knowledge about a health of a family member which that individual did not possess. As shown by the case studies, most research is using sample collections does not attempt to identify an individual participant's genotype. Instead, data is gathered at a population or family level. However, there is an argument that participants should have the right to know their genotype, regardless of the social consequences. Similarly, there is an argument that people have the right not to know.

Members of the medical profession involved in caring for patients/ participants may also have a legitimate interest in knowing the result of any genotyping. Similarly, other third parties, such as insurers and employers may find genetic information of commercial benefit to them.

- Do research subjects have a right to know information that affects them? Should studies be designed to enable this?
- Do purely anonymous studies run counter to safeguarding individual health?
- Do participants also have a right not to know?
- Should information be fed back to genetically related non-participants?
- Should it be passed onto the participant's doctor in situations where their healthcare could be improved?
- What access to information should be given to other interested third parties (e.g. employers, insurers)?

5.5.5. Potential socio-economic impacts of research

One of the most important questions for social scientists is trying to assess the potential impacts of this type of genetic research. These might be felt in a number of areas, including, healthcare, personal identity, health policy, discrimination and in the competitiveness of UK industry. As mentioned above, there will be a large amount of diagnostic information about the association between having a particular genotype and getting a specific disease. However, diagnosis will be available long before effective therapies are introduced in many cases. If this information were widely available it could lead to the creation of new classes of 'patient' (the asymptomatically ill or disabled) for whom little could be done. The widespread use of genetic information would also have important implications for health policy and the emphasis given to drug based therapies, perhaps at the expense of environmental protection and social improvements.

Much discussion has already taken place about the potential for discrimination which the introduction of new genetic screening and diagnostic technologies might present in the areas of employment and insurance. Functional genomic research might significantly increase the possibility of this occurring either as a consequence of a persons involvement in research or as a result of the introduction of widespread genetic testing. However, it must be stressed that significant clinical and commercial benefits are likely to result from research involving sample collections. The public policy objective must therefore be to regulate the creation and dissemination of genetic information is such a way that the maximum benefits for healthcare and industry are ensured, whilst protecting research subjects and civil rights.

- What is the utility of predictive genetic information in cases where no therapy exists?
- What are the implications for health and public policy of changing concepts of the body and illness causation?
- How real is the potential for discrimination based on this new genetic knowledge? What measures can be adopted to protect people's civil rights?
- How can the application of new genetic knowledge in healthcare and its incorporation into new technologies be regulated in such a way as to strengthen the development of the UK biotechnology industry, whilst minimising the adverse consequences for society?

- Finally, what is the future for collective healthcare provision in the UK in the context of genetics research which is intrinsically concerned with individual factors which contribute to differences in health?