Ethical Issues and GenomEUtwin

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The post-genomic era is witnessing a proliferation of large-scale and population based genetic and genomic research projects. Many countries have or are establishing research biobanks and, as with GenomEUtwin, there is great interest in building multinational projects that link genotypic and phenotypic information from different centers. Clearly, the conduct of these projects raises multiple ethical issues, and the knowledge generated will continually recast the ethical, legal and social implications (ELSI) of such research. Maximising the scientific profit from this work while minimizing the risks to the participants requires full integration of ethics components into the structure and functioning of these projects. GenomEUtwin is organized around five intellectual cores, including an Ethics Core which operates across the entire project. This paper describes the role of the Ethics Core and presents an overview of the guidelines on which the principles followed in GenomEUtwin are based. We outline the major ethical concerns of our project and highlight complexities arising from diverse national legislations. Finally, the role of empirically based ethics research is discussed for understanding the ethical, legal, social and economic implications of human genetics and genomics research.

Large-scale genomics research promises to help elucidate how biological systems function and interact with a host of environmental factors, both in healthy development and in the pathogenesis of disease. Novel methodological approaches coupled with faster and cheaper genotyping and phenotyping tools will generate information critical to understanding disease etiology, diagnosis, and the tailoring of treatment and prevention. In these endeavors population-based studies, such as GenomEUtwin, are critical to identify predisposing alleles and verify their significance in the population at hand as well as for exploring gene-environment interactions. However, these advances carry the potential to undermine the very paradigms and technologies upon which they are built if the resulting genetic information is misused (e.g., health-insurance discrimination) or causes detriment to individuals, families and society. This was recognized from the beginning by the planners of the Human Genome Project (HGP) who developed an ethical, legal and social implications (ELSI) program to promote research, education and outreach surrounding ethical, legal and social issues of human genetic and genomic research.[1]

Although the importance of articulating ELSI issues is receiving increased attention, neither empirical investigations into the most urgent ethical issues, nor the establishment of ethical procedures used in empirical research has been able to keep pace with the unprecedented acceleration in genomics technology. This arises, in part, because the post-genomic era is confronting individuals, families, societies, policy makers, politicians, legal experts, educators and researchers with unforeseen problems and concerns. Optimizing genetic and genomic knowledge accompanied by minimizing risk is a complicated task. There is considerable context dependency associated with, for example, sociocultural factors, the genetic basis of the disease under study, age, national health care and legal systems and our knowledge of etiology and treatment. For instance, when prevention is possible, as in the single gene disorder PKU, ethical concerns about testing for individuals at risk are straightforward and neonatal screening is widely acceptable.

Nevertheless, knowledge generated from these studies will raise new and specific ethical issues that require full integration of genetics and genomics into public health research agendas (Beskow, 2001). Some of the ethical issues are common across studies and underline the need for harmonizing guidelines and regulatory frameworks in order to pursue international projects. Other issues may be more specific to each study and researchers will need to evaluate such potential in the planning and development phases of their studies. For example, GenomEUtwin poses unique questions because an identical twin who consents to genotyping has, de facto, provided DNA for their co-twin.

GenomEUtwin currently includes research centers from Australia, Denmark, Finland, Italy, the Netherlands, Norway, Sweden, and the United Kingdom. The purpose

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of this paper is to provide an overview of the ethical issues that confront such multinational genetic and genomic projects and to describe the approaches adopted by GenomEUtwin for handling these issues. First we describe the role of the Ethics Core associated with our project, then we summarize European and other guidelines which provide the backdrop for the principles followed in GenomEUtwin. Next we outline the major ethical concerns of our project and highlight complexities arising from diverse national legislations. Finally, the importance of empirically-based ethics research is discussed in order to further our understanding of the ethical, legal, social and economic implications of genetics and genomics research.

The GenomEUtwin Ethics Core

As described elsewhere in this volume the main research goal of GenomEUtwin is to identify genes that predispose to common diseases. A project of this magnitude, with study samples being collected in several countries, poses multiple ethical dilemmas. An EC regulatory framework does not yet exist for ethical issues and consent for genetic studies. To help address and implement the ethical issues raised in this project an Ethics Core was established as an integral component of GenomEUtwin. The Ethics Core is composed of representatives from each participating center who are knowledgeable about their respective country's ethics code, and is reinforced by internationally acknowledged experts in medical ethics and biobanking.[2]The principles followed by the Ethics Core for addressing key ethical issues related to data collection, storage, consent, use of samples and secondary use of samples are based upon a number of documents as articulated in the next section.

A key activity of the Ethics Core is to harmonize ethics protocols across centers and make public the procedures and products related to our activities. This involves identifying commonalities and differences between the participating countries regarding ethical regulations (e.g., informed consent) so that our procedures and products (e.g., consent forms) can be standardized yet modifiable in accordance with national regulations. Such information will be used to formulate templates for informed consent and for research applications for approval by local ethics boards. These forms, along with the ethical guidelines, will be published in a project ethics manual and posted on the project website along with other background information. The Ethics Core will keep track of the local ethics committees' authorizations and opinions and give advice to local centers when applying for local approval, if requested. In conjunction with local ethics committees the Ethics Core will also develop procedures to handle special circumstances that may lead to release of genetic results to certain participants.

Many of our ethics related procedures are still in the developmental phase, but project after project is faced with the same ethical issues and concerns; the development of standardized guidelines will greatly facilitate the type of genetic research and biobanking procedures that will be necessary to elucidate the etiology of complex disease. A unique feature of GenomEUtwin is the prospective cardiovascular cohort component: MORGAM. The rationale behind its inclusion is that candidate genes for cardiovascular disease identified in the twin studies can be tested prospectively within MORGAM. The tasks of our Ethics Core will benefit enormously from the work already completed and the ethics manual generated from our partners associated with the MORGAM project. MORGAM has developed other tools such as a standardized Ethical Clearance Letter which must be produced to lend assurance to the Coordinators that the necessary ethical safeguards are in place, and a simple Material and Data Transfer Agreement which must be completed before the shipping of data and samples to the central laboratory, or between the central laboratories and other participating laboratories. It is planned that the Material and Data Transfer Agreement developed in MORGAM will be adopted for use more generally within GENOMEUTWIN.[3] Training young scientists and researchers on the project also comes under the auspices of the Ethics Core. This includes organizing ethics modules for courses in our training and mobility component and working to foster networks between groups, with established expertise in bioethics, and the participating centers. The Core will meet whenever necessary; however, at least once a year a meeting is held with special emphasis placed on ethics training of young scientists participating in the Project.

The Ethics Core is also instrumental in forging research networks that connect researchers associated with GenomEUtwin with experts in ethics and related fields. Along these lines the Ethics Core writes proposals applying for supplemental research funds to recruit young scientists who can help develop and conduct newly formulated research projects investigating ELSI issues.

Overview of Guidelines on Biomedical Research and Ethics with Special Emphasis on Genetic Research and Biobanks

A substantial number of regulations and guidelines exist concerning bioethics and research and derive from a wide range of sources ranging from international agencies to national legislation to statements issued from professional societies. The sheer number of recent bioethics documents emanating from these diverse sources illustrates the necessity for standardization and harmonization of ethical research protocols in genetics. While it is not our purpose to provide a comprehensive overview of these various documents, we do present some background information concerning the documents most essential for the development of the European guidelines upon which we base our ethical procedures in GenomEUtwin. Some of the debate and concerns raised by these documents illustrates that the field is far from unified, a situation that many researchers grapple with in project development.

For more than 2000 years the medical profession has regarded the Hippocratic Oath as the gold standard for good medical conduct. But, biomedical research ethics has a much shorter history of regulations, the oldest dating to The Nuremberg Code (1946)[4]. In 1964 the World Medical Association (WMA) agreed upon the first Declaration of Helsinki[5] which provides guidance for all medical research involving human subjects, including identifiable human material or identifiable data, including DNA from

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biobanks. It states explicitly that considerations related to the well-being of the human subject should take precedence over the interests of science and society. The Declaration distinguishes between research subjects and patients who can gain from the research versus those who can not and emphasizes the necessity to view research without benefit to the research subjects rigorously such that the absolute risk to subjects participating in research is minimized. This document has been amended several times, the latest in 2002.

The Council for International Organizations of Medical Sciences (CIOMS) published in 1982 and updated in 2002 the International Ethical Guidelines for Biomedical Research Involving Human Subjects.[6] These guidelines are highly congruent with the Helsinki Declaration, although much more specific and comprehensive. A number of issues remain controversial (e.g., the necessity for consent and of informing patients of their personal results). Currently, many of these guidelines are used by several European countries. In response to ethical concerns of particular relevance to epidemiological studies the CIOMS also developed in collaboration with WHO International Guidelines for Ethical Review of Epidemiological Studies[7], which were published in 1991.

In 1996 the Council of Europe issued the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to Application of Biology and Medicine: Convention on Human Rights and Medicine.[8] Among other things, this convention states that predictive genetic testing and intervention on the human genome must only take place based on a health-related indication or as part of biomedical research. In 2001 the European Parliament's Temporary Committee on Human Genetics and Other New Technologies in Modern Medicine issued a Report on the ethical, legal, economic and social implications of human genetics[9] that was based upon a background document and a draft report which had been considered to be balanced and insightful by many researchers in the field. However, the final report was quite restrictive with many amendments and recommendations regarding several highly debatable issues (e.g., therapeutic cloning) including that the EU guidelines should have priority over national guidelines (i.e., to relinquish the sub- sidiarity principle of the EU). The report was voted down by the European Parliament in November 2001.

In 2002 WHO's Advisory Committee on Health Research also issued its report on Genomics and World Health.[10] The section on the ethical implications of genomics is particularly concerned with the risk of disparity in health care across countries, due to the expense related to new biotechnology and information technology, and the risk of neglect of diseases in the poorest countries of the world.

The completion of the Human Genome Project and its accompanying explosion in genetic knowledge and research has created greater interest for access to biological materials from large numbers of subjects and families. Consequently, attention is focused on possibilities for storing these samples (i.e., biobanks). A number of European countries now have guidelines and opinions issued by medical research councils or ministries; some of these are referred to here and those of relevance to the countries participating in GenomEUtwin are referenced on our web page. Articulating the ethical issues involved in such biobanks is not straightforward and has been handled differently by different countries and projects. For instance, several research projects have been carried out in Sweden to seek the kind of biobank management that will satisfy the interest of both the research community and the general public. Results were recently published in the book Biobanks as resources for health (Hansson, 2003). The UK Biobank project, a proposed large-scale study of 500,000 individuals that will investigate genetic, the environmental and lifestyle factors on common diseases of adulthood, has followed a somewhat different route and the deliberations generated from an ethics consultation workshop held in 2002[11] will serve as the basis for developing the ethical framework for the Biobank.

In addition to national publications an EU opinion was released (1998) on Ethical Aspects of Human Tissue Banking.[12] This document represents the opinion of the European Group on Ethics in Science and New Technologies regarding: the need to protect health of both donors and recipients of tissue, respect of bodily integrity of donors, procuring informed consent, respect of privacy and confidentiality of information collected, prevention of possible discrimination and promoting solidarity and tissue availability in Europe. Furthermore, this Group reserves tissue banking activities to public health institutions or non-profit organisations. An EU workshop on optimisation of biobanks held in Oslo, Norway in January 2003[13], recommends standardisation of guidelines for exchange of biological material within Europe, consideration of the wide European differences when performing ethical review and informing donors, ethical review of all collections of human material, bridging historical biobanks with freshly stored samples and registry data, development of common protocols and support of interdisciplinary European networks.

Areas of Major Ethical Concerns and GenomEUtwin

The major ethical issues connected with research studies that involve the collection and storage of biological samples originate from the principles of informed consent, storage of biological samples, data security and protection of the confidential information relative to donors, and non-tradability of the human body (Deschênes et al., 2001). In addition, questions of commercialization and providing feedback to participants need to be addressed in project planning.

Informed Consent

Informed consent is a basic tenet of bioethics and an expression of the fundamental principles of an individual's autonomy and respect for freedom. The key documents that address fundamentals of medical ethics, at national and international levels (Lenoir & Mathieu, 1998), refer to the duty to obtain voluntary and informed consent after providing individuals with appropriate information. For example, Article 1 of the Nuremberg Code recognizes free

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and informed consent as fundamental to human research (The Nuremberg Code, 1946). Guidelines on the consent requirements, in the case of human tissue banks can be inferred from both generic documents (e.g., the Helsinki Declaration (World Medical Association, 2000; CIOMS, 2002) and from specific documents on genetic research (e.g., "Statement on informed consent for genetic research" of the American Society for Human Genetics, American Society for Human Genetics, 1996). These documents basically agree upon the principles identified, with regard to both consent and the other requirements.

The principle of consent provides that the individual will be explicitly informed of the purpose of data collection, the confidentiality of the data, the measures taken to protect confidentiality, who will have access to the data, the transfer and disposal of data, and the potential secondary use of data. The controller of the data is required to institute appropriate safeguards for personal data stored for research use.

Consent forms for sampling and storage of biological material shall therefore specify the following:

- possible risks and harms to the participant related to conduct of the research
- purposes for which samples are taken
- purposes of the storage of samples
- methods and techniques used
- terms under which the confidentiality of the data and anonymity are granted
- selection of structures for the analyses and storage of samples
- duration of the storage
- methods of withdrawing consent, if possible or requesting to eliminate one's sample from a human tissue bank
- use of a sample in case of the donor's death.

An aspect of consent with peculiar connotations for human tissue banks, and with which GenomEUtwin may well be confronted in the future, involves samples for which individuals are unable to express their consent. This could arise if individuals die in the course of the research or become too ill to be able to provide informed consent. The "Convention on Human Rights and Biomedicine" states: "Where, according to law, an adult does not have the capacity to consent to an intervention because of a mental disability, a disease or for similar reasons, the intervention may only be carried out with the authorization of his or her representative, or an authority, or a person or body provided for by law. The individual concerned shall as far as possible take part in the authorization procedure" (art. 6).

Updating of Consent

An important aspect for any human tissue bank or collection of genome-wide scans concerns the consent for potential future applications that were not envisaged at the initiation at the project. This has particular implications for GenomEUtwin because of its scientific objectives and the probability that this platform will serve for many new projects in the future. A typical scenario may be that new interests and applications emerge while the original project is underway; this raises the question of updating consent procedures. Many documents are explicit in this regard; among them, reference can be made to the "Convention on Human Rights and Biomedicine" of the Council of Europe, which states in article 22 that: "When in the course of an intervention any part of a human 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" (Council of Europe, 1996). This article also applies to blood samples. Other documents specify a duty to only use the samples present in human tissue banks only for the purposes for which consent was given. In this respect, among the various existing texts, reference should be made to the document entitled "Ethical aspects of human tissue banking" of the European Group on Ethics in Science and New Technologies (European Group on Ethics, 1998).

Between country differences exist in the regulations regarding renewal and updating of consent procedures. Some countries are currently re-evaluating and reforming these regulations. For example, in Finland *The Act on the Use of Human Organs and Tissues for Medical Purposes* (2001) allows a tissue sample collected for medical research to be used for another medical research project, but only if the research subject has given his or her consent to it. Therefore, a new consent must be obtained if the original consent does not cover the new use of the sample. However, a working group of the Sub-Committee on Medical Research Ethics of the National Advisory Board on Health Care Ethics has recently (Autumn 2002) issued a report on DNA samples in epidemiologic research where they propose that some national board/committee/authority should be allowed to give consent to further research if the person who has given the sample can't be contacted (with reasonable efforts if they are still alive). So far this proposal has not led to any concrete legislative proposals, but this issue will be further considered at the Ministry of Health. It is possible though to obtain consent for rather broad definitions (e.g., in Denmark it is not necessary to specify in the consent form each candidate gene or SNP that is of interest for study). Thus it is possible after years of banking the DNA to use it for new tests if these are considered to be covered by the original broad definition. These circumstances may, however (depending on the country), need to be judged by the officially appointed medical ethics committee prior to the analyses. A related issue is that of data storage when the proposed analyses are finished. In many countries the consent form should describe what will happen with remaining biological samples once the research has been completed, and it may also be required that the biological samples are destroyed. Individuals should be made aware if, and for what reason, biological material is stored.

Confidentiality and Risk of Discrimination

Data confidentiality is one of the basic requirements for research involving humans. The current European legislations on data confidentiality and security are derived from directive 95/46/EC of the European Parliament and of the

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Council "on the protection of individuals with regard to processing of personal data and on the free movement of such data", and from recommendation R(97)5 of the Committee of Ministers to member states "on the protection of medical data". The directive requires individuals consented for a study to be informed on the collection, processing and storing of personal data.

Issues of data confidentiality are closely linked to the ownership of the data. The question "who owns the data?" is not specifically addressed by most European law and may differ from US law in this regard, where the biological sample may still "belong" to the subject. In their recent guidelines the United Kingdom Medical Research Council (UK-MRC) states that the UK-MRC may retain the formal responsibility for large multi-center collections or research-directed databases, though the day-to-day care for the databases will remain with the institutions that collected the data. In this sense the interpretation by the UK-MRC of the status of personal data may most closely reflect the intention of most European legislation; tissue samples are seen as gifts or donations and property rights and control of the samples are automatically transferred to the recipient of the gift. However, the donor has the right to restrict the use of the donation. The EU Directive 95/46/EC states that personal data need to be governed by one responsible person or institution. For the countries participating in GenomEUtwin the institution or university is responsible for the data, which is preferable because it prevents problems that may arise if an individual responsible for the data leaves an institution. Responsibility for the database also incorporates the obligation to safeguard the confidentiality of the data. Organisations that maintain databases with personal information are typically held responsible for the safety of the data, for instance by encoding the data and using specialised encrypting software. Although institutions or individuals are held responsible for the personal data registers, they are not allowed to share the information with a third party without informing the individuals involved. An exception is data which are stored unlinked; that is, information on the identification of the individuals is unlinked from the phenotypic and genotypic data, making it impossible to trace the individual donating the information. Biological samples may never be sold for a profit but intellectual property rights may be sold or licensed.

In biological banks where DNA is stored, information is potentially much broader than was purposely collected for the initial objectives of the study. Such potential grows as knowledge in the genetic field develops. Therefore, biological banks are actually banks of sensitive data, capable of drawing the attention of many outside interests, with objectives that are varied and distant from the diagnostic, therapeutic and research purposes proper for medical and biological sciences (e.g., insurance companies, banks, employers, and law enforcement agencies). The operational criteria which have to be met can be drawn from both more generic principles expressed in declarations, treaties and other documents of bioethics (Lenoir & Mathieu, 1998), and from specific documents, such as "Genetics and privacy: a patchwork for protection" commissioned by the California Health Care Foundation (Hustead et al., 2002). In many countries, this issue is ruled by specific regulations (Byrne, 1997). Some concepts governing the protection of personal data can be gleaned from the bulk of these documents:

- monitor the access to data
- supervise the purposes for data storage and use
- control the proportionality between quantity and quality of the data stored with regard to the aims of their storage
- check that the storage time does not exceed the necessary period
- grant an individual the access to his/her data and the possibility to check, integrate or block them
- grant "traceability": it should be possible to trace the origin of data and to know the transmission modes.

Data Confidentiality in GenomEUtwin

In developing the GenomEUtwin databases, issues of data confidentiality and protection are complicated by diverse legislation concerning privacy and data confidentiality in the participating countries. For reasons of data confidentiality GenomEUtwin will separate the phenotypic database from the genotypic database to ensure greater security of the data. Genotypic and phenotypic data will only be merged for analytical purposes, and the ability to do the analyses will be regulated by the Database and Statistical Cores, with the permission of the twin registries.

A central genotypic database will be physically located at the National Public Health Institute. The genotypic database will include both microsatellite and single nucleotide polymorphism marker data, which will be contributed by four genotyping facilities: the Genome Center and the Department of Molecular Medicine at Uppsala University, the Finnish Genome Center, and the National Public Health Institute of Finland. The individual DNA samples included in the project are labeled with a GenomEUtwin ID number, which will be different from internally identifiable data at the respective study centers. Each twin registry will keep their own internal study IDs and keys, linking the study IDs to personal identifiers and other data, will be kept secure under their own security policies. Genotypic data will be encrypted before transfer from the genotyping centers to the general GenomEUtwin genotypic database or to and from the registry centers. All databases will be protected by firewalls, and will have a password-protected access. The genetic data will not be released to participants, except under special circumstances and in consultation with the local Ethics Committees.

Extensive phenotypic data have been and are being collected by each twin registry participating in the GenomEUtwin project. These data are administrated and secured by each respective twin registry (for the latest reference on the twin registries see Boomsma et al., 2002; Harris et al., 2002; Hopper, 2002; Kaprio & Koskenvuo, 2002; Pedersen et al., 2002; Skytthe et al., 2002; Spector & MacGregor, 2002; Stazi et al., 2002). The Database Core is working in a stepwise manner to develop a long- term solution to secure the database. For phenotypic data this entails a two-stage

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process, the first stage is creation of a common data structure and the transfer of encrypted files to be used in a prototype database. GenomEUtwin will not construct a central phenotypic database. Rather, the ultimate goal is the creation of transient analyses-specific phenotypic databases that will be analyzed and then deleted at the end of analyses. These transient databases will be encrypted and password-protected and are only accessible by the researchers participating in the project. The database core is investigating whether it is possible to also decrypt the local databases before they are connected by distributed SQL. A procedure for testing this will soon be set up between Helsinki, Stockholm and London. For more details on the structure of the GenomEUtwin databases see the paper by Litton et al., in this issue.

Responsibility and Safety

Problems of responsibility arise during the entire storage period of material in human tissue banks. Data protection should help prevent the risk of a discriminatory use of information. This problem has worsened in past years, mainly because of a greater resort to genetic testing. In particular, medical information disclosed to employers, and insurance companies could be used to penalize individuals or groups of individuals. Therefore, human tissue bank managers will take all the necessary steps in order to prevent an unauthorized use of information. In this respect the human tissue bank data managers plays a particularly important role in preventing unauthorized uses of data. Human tissue bank managers are entrusted with managing control activities, compliance with professional codes and international directives, and ensuring confidentiality. In order to grant the respect for all the ethical and scientific requirements in the management of human tissue bank, the choice of a manager is fundamental (Knoppers et al., 1998). Ethics committees are entrusted with the main responsibility of granting their approval for the setting up of human tissue banks. The Committees should be consulted if the human tissue bank is to be used for purposes different from those for which it had initially been set up and for which all participants gave their consent. Although GenomEUtwin is not a centralized human tissue bank, in multicenter studies, such as GenomEUtwin, it is appropriate to have a manager for every independent structure. The role of the manager is also important for monitoring of biological safety. In fact, the manager will monitor the observance for safety rules, since biological material can constitute a potential route for spread of disease. The protection from biological risks will concern all actors (i.e., donors and medical and non-medical staff). Among other things, safety requires "traceability" to be granted (i.e., if need be, it should be possible to track down the donor, at any time).

Feedback of Results to Participants

According to the national legislations of each country participating in GenomEUtwin, individuals also have the right to know what data are available on them in the database. However, each legislation does not provide strict rules for the feedback of research results to participants on an individual basis but states that informed consent should describe to participants whether they will receive feedback and the type of feedback they may expect from the research. In GenomEUtwin the study results are intended for specific scientific purposes only. Therefore the general principal is that genotypic or other genetic data will not be released to participants and consent has been based on this information. If special circumstances arise regarding the request for information then these will need to be handled on a case-by-case basis with input from the Ethics Core in conjunction with local ethics committees. It must be emphasized that the information produced by this project does not meet clinical service laboratory standards. Therefore any information released must to be replicated on a fresh sample of the subject's tissue (this applies to all samples because of the possibility of mislabeling, but particularly to DNA samples) in a setting providing: a) pre-laboratory counseling, b) adequate confirmation by a clinically-approved laboratory and c) post-laboratory counseling with quality control in place.

National Legislations

Because GenomEUtwin incorporates data from various countries it presents an excellent platform for the comparison of different legislations and also presents many challenges that confront multinational studies. Comparison of legislations is a task to be undertaken by experts versed in the fine details of international law and will not be addressed further here. However, for those planning new projects it is important to meet with local ethics boards, involve national ethics experts in the project from the beginning and consider whether your project must address unique concerns not commonly addressed in the extant guidelines and documents. Furthermore, it is important to dedicate time early in project development to mapping out the similarities and differences in the relevant legislations from participating countries. This information is essential to preparation of local ethics applications and consents and updating of consent forms for new uses of the biological samples. An early activity of the Ethics Core was to survey which twin cohorts could share previously collected DNA, completed genome scans and phenotypic data to GenomEUtwin. Denmark and the UK were the only countries in a position to contribute data almost from the start (Denmark needed to simply amend their approval applications to cover the transfers of samples). The Danish and UK scientific ethics committees will approve projects with broad aims and do not require that every phenotype for which gene searches may be conducted be specified in the consent forms. Because the Danish and British twins have already consented to having their DNA samples used for a wide variety of studies (e.g., longevity, diabetes, migraine, osteoporosis, CVD and related risk factors) the phenotypes of interest in GenomEUtwin were already covered by the existing approvals from the relevant data protection agencies and ethics boards. The GenomEUtwin Ethics Core is currently working on summarizing the inter-country differences in order to proceed with the templates for consent, updating of consent and ethics applications as described above. Examples of each country's consent forms will also be posted on our website. Even though a common set of

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ethical guidelines reflecting the national regulations of the participating countries does not exist, and some countries have not incorporated the EU Directive, all countries address the same general issues in the form of various national laws and regulations, which differ primarily with respect to the extent to which these aspects are legalised. Although it would be too lengthy to catalogue these differences, copies of these and related documents are listed by country on our webpage.[14]

It is important to note that all data stored within the twin registries are classified as personal data, including genetic information when obtained for research purposes and not for medical treatment. The countries involved in the GenomEUtwin project have restricted the use of personal data by law. This law may be differentially referenced in the different countries (e.g., the *Public Administration Act in Norway*, but for clarity we will refer to it as the *Data Protection Act*.) Regardless of the recommendations from the larger community, the law of each country ultimately determines the restrictions imposed on the researchers. The distinction between guidelines and actual legislation is well illustrated by the European Union Data Protection Directive. This directive, which was passed by the EU in 1995, provides guidelines for the handling of personal data, which should have been implemented by all Member States of the European Union by 1998. The set of laws introduced by the Act are the minimum laws required for EU countries and therefore differences between countries may still exist as some countries adopt stricter laws than other countries. All GenomEUtwin participants have either incorporated the EU Directive in their laws or are in the process of doing so. However, not all European countries have presently incorporated these guidelines in their laws; as such local institutes are bound by their country's laws and not by the EU guidelines. Many institutions may impose additional guidelines for research, resulting in more strict conditions on research procedures.

The transfer of information from European Countries to others countries, as stated in the EU Directive, is legally restricted to those countries or international institutions which provide appropriate protection of personal data. The recent adaptation of the data protection law in Australia enabled the exchange of personal data between the EU and Australia. In some cases transfer can still take place, for instance, if the person involved has given permission for the transfer. Consequently, the progress of any particular multinational project could be hindered depending on the differences in national legislations of the countries comprising the project.

Empirical Research into Ethical, Legal, Social and Economic Implications of Human Genetic and Genomic Research

The importance of establishing empirical research surrounding ethical, legal and social implications of genetic and genomic research is gaining momentum. As mentioned above, the planners of the Human Genome Project were acutely aware of the need to establish an ELSI component.[15]More recently, the Norwegian Functional Genomics Platform (FUGE) has set aside funds to explore ethical, legal and social issues of human biobank projects.[16] The function of these ELSI programs is to foster scientific research that identifies, articulates, and examines ELSI issues in human genetic studies in parallel with research in the basic sciences. The research solicited under ELSI programmes spans a large array of topics surrounding genetic research (e.g., privacy and fairness in the use and interpretation of genetic information, informed consent, commercial use of genetic information, and education). Furthermore, the scope is very broad, ranging from questions aimed at understanding individual-level processes to those concerned with larger sociocultural and societal issues. Such research will be critical for integrating new knowledge into public health agendas and health care practice. Most ELSI research requires expertise in areas (e.g., law, bioethics) and study designs (e.g., qualitative methods) that are not traditionally associated with the cohort studies comprising GenomEUtwin.

One of the goals of the Ethics Core is to help stimulate empirical ELSI research. To achieve a fuller understanding of these ELSI-related issues it is vitally important to conduct population-based research where the participants in the genetic study are also part of the ELSI research. From a research perspective GENOMEUTWIN offers unique data to analyze ethical, legal, social and cultural impacts of register-based and genetic studies. The multinational data provide a natural experiment to test cultural differences, and explore how differences in national standards and legislation affect subjective understandings of genetic research and participation in these studies. This approach will help to map how ethical and social problems and perceptions of genetic research may vary between different societies. It also will provide the possibility of setting some accepted standards and codes of practice for genetic epidemiological studies at the European level. Because identical twins share all of their genes, a twin design permits the unique, natural, and extreme study of familial perception of genetic predisposition. One of the most critical challenges in the endeavor of ELSI research will be the identification and articulation of the specific research questions to be studied and implementation of the most effective design to answer them. This involves interdisciplinary approaches, often combining areas as diverse as law, philosophy, psychology and medicine.

We have outlined key ethics-related issues associated with GenomEUtwin. Many of these are common to other genetic and biobanking projects. But some of these issues are moving targets, as science progresses new ethical considerations will be brought to light, and others may become trivial. Today's consensus on immediate issues may quickly become outdated. Because we are unable to foresee all the new concerns that will arise research is needed to continue to articulate these issues and integrate them into public health agendas. Although the knowledge needed to conduct ELSI research is seldom part of the normal repertoire of the geneticists' toolbox, inclusion of experts who can design ELSI projects in tandem with genetics research will help maximize the potential of the data. GenomEUtwin will produce an enormous amount of information on the interaction of genetic and environmental factors contributing to

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human health. But we are also obligated to mine it for the unique contributions it can make to ELSI research and to ethical protocols within Europe and, perhaps, worldwide.

Endnotes

1. Information about this is available from http://www. genome.gov/10001618
2. see http://www.genomeutwin.org for a description of the core and its members.
3. These documents will be available shortly on the MORGAM website http://www.ktl.fi/morgam/
4. The Nuremberg code is available from http://ohsr.od.nih.gov/nuremberg.php3
5. Available from http://www.wma.net/e/policy/b3.htm
6. The international ethical guidelines for biomedical research involving human subjects are available from http://www.cioms.ch/frame_guidelines_nov_2002.htm
7. International Guidelines for Ethical Review of Epidemiological Studies are available from http://bioetica.bibliotecavirtualensalud.org/I/epidem.htm
8. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to Application of Biology and Medicine: Convention on Human Rights and Medicine is available from http://conventions.coe.int/Treaty/en/Summaries/ Html/164.htm
9. This report on the ethical, legal, economic and social implications of human genetics is available from http://europa.eu.int/comm/research/biosociety/pdf/pe_genetics.pdf
10. This report is available from http://www3.who.int/whosis/genomics/genomics_report.cfm
11. The UK Biobank project, a proposed large-scale study of 500,000 individuals that will investigate genetic, the environmental and lifestyle factors on common diseases of adulthood, has followed a somewhat different route and the deliberations generated from an ethics consultation workshop held in 2002 http://www.ukbiobank.ac.uk/documents/ethics_work.pdf
12. Ethical aspects of human tissue banking is available from http://europa.eu.int/comm/european_group_ethics/docs/cp11_en.pdf
13. http://www.fhi.no/hvaskjer/biobanks_workshop.html
14. http://www.genomeutwin.org
15. http://www.genome.gov/10001618
16. http://www.forskningsradet.no/fag/andre/fuge/forskningsmidler2003/

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