

**Report of the Bioethics Advisory Committee of
The Israel Academy of Sciences and Humanities**

**Population-Based Large-Scale Collections
of DNA Samples and Databases of Genetic Information**

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Chapter 1. Why Is This An Issue?

What is the purpose of large-scale Population-based DNA Collections?

1. One of the ultimate aims of the study of human genetics, is to understand the function and naturally occurring variations of human genes as these relate to their phenotypic manifestations, including various human attributes, and in particular, diseases which affect the human species. Study of the relationship between genes and diseases began with cloning genes for infrequent, mostly monogenic, Mendelian disorders, mainly through analysis of families in which these diseases occur. The genes, in which the disease-related changes occur, were identified through techniques known as genetic **linkage** and positional cloning.
2. More recently, the possibility of unraveling the genetics of many more common diseases may be nearing our grasp thanks to the near-completion of the Human Genome Project (HGP). Most common diseases that have a genetic background are complex and not due to one gene defect, but are multigenic and multifactorial (including interactions between genes and environment). Understanding the genetic basis of common human illnesses (such as cardiovascular diseases, diabetes, asthma, neurological diseases and cancers) is likely to have a major impact on public health and holds enormous potential for pharmaceutical and other therapeutic modalities.
3. The novel scientific approach for identifying genes involved in common diseases can be simplistically described as a comparison of the genetic variations (polymorphisms) between healthy persons, and persons affected with the disease in question. By analyzing the polymorphisms throughout the entire genome, correlations with occurrence of disease can be established by the technique of genetic association analysis.
4. Because these comparisons are statistical in nature, in order to be meaningful, they must be performed on a large scale (many thousands of samples). They may also be most powerful when carried out in cohorts of patients and healthy controls having a common ethnic origin so as to minimize unrelated variations. Hence, the need to establish population-based large-scale DNA collections. An example demonstrating the power of this new approach to the study of the genetic basis of common disease has been the recent publication of a highly significant association between Schizophrenia and a certain gene haplotype (Shifman et al, 2002).
5. The said collections include actual samples from which genetic material (DNA) can be derived, together with databases linking the samples to medical and other forms of information obtained from the large numbers of persons involved in the study. After the genetic testing is performed on the DNA samples, another database linking the genetic information to the medical information is created. Some of the medical information may need to be gathered over time, requiring continued linkage of samples with genetic, medical and personal information of participating individuals.



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Ethical issues raised by large-scale Genetic collections and databases

6. The rights of individuals with respect to their DNA samples and genetic information derived from them are protected in Israel by the Genetic Information Law, 5761-2000. The Law and existing ethical guidelines cover most issues of informed consent, confidentiality and rules of accession relating to either identified or non-identified DNA samples or genetic information in the usual individual or family-based, small-scale, collections.
7. The establishment and maintenance of large-scale databases, amassing sensitive genetic and medical information raises new ethical issues (Beskow, et al, 2001, Anas, 2001, Issa, 2002). One of the major issues is the status of the medical and personal data that are linked to the genetic collection. Does this linked information confer a status of identifiable genetic information? Or, else, can it be coded in a way that anonymizes the data, while at the same time allowing the continuous link to be maintained? Considering that genetic association studies are likely to require repetitive comparison of the medical information with the genotyping data in various subgroups of individuals tested, the modalities of access to the databases must be addressed very precisely. Keeping in mind the Genetic Information Law, guidelines for large-scale, population-based collections have to relate to confidentiality of genetic and medical information, to consent of participants for present and future genetic testing, and to eventual release of any medical or personal data.
8. Informed consent and confidentiality are crucial to the voluntary participation of any individual in medical research, and in general, the usual guidelines are also applicable to participation in large-scale genetic association studies. However, with such genetic databases, there are particular issues which need to be recognized. Consent for participation in association studies must be broad because the acquisition and use of genetic database information is still evolving, a very wide range of studies can be performed, and not all of them can currently be envisioned. This differs from the usual consent, which is specific. Use of existing collections such as pathology samples or biopsies to extract DNA, raises questions of whether the consent given before surgery did in fact include genetic testing.
9. The size and scope of databases may raise serious confidentiality issues, because of the large amounts of data collected on each individual, in the form of an easily searchable matrix. Individual rights must be protected in this context, even in cases where breaching confidentiality may be seen as serving a goal beneficial to society, such as forensic or other types of judiciary investigations. However, there might be emergency situations, such as casualty identifications, where the entry into large-scale genetic databases could be viewed as justified despite the potential harm to private confidentiality.
10. In addition to protection of individual rights, the large-scale population based-genetic databases raise issues related to the protection of the collectivity, namely the legal and moral rights of entire social groups. Genetic profiling of a collectivity that can be defined by ethnic or national origins could lead to risks of stigmatization of all those who belong to the collective. Worse, this could lead to discrimination in various forms - moral, physical or economic. Some have also raised fears relating to security, such as using genetics to identify means by which a collective, or a nation, could be aggressed and militarily harmed.



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Commercialization of genetic collections and databases.

11. Other ethical issues pertain to ownership of the samples and of the information linked to them, with the ensuing questions related to commercialization or “privatization” of the databases, and the allocation of benefits and profits stemming from the databases. It must be understood that the large-scale genetic collections and databases have, almost immediately, an intrinsic commercial value even before they produce a single diagnostic test or therapeutical drug.
12. Studying the genetics of common diseases holds enormous promise, but this promise has yet to be fulfilled. To date only a handful of studies have resulted in unequivocal identification of a gene related to a specific disease. Thus, at the scientific level, the field of large-scale genetic association studies is at an early stage that would not usually be considered sufficiently mature for commercial/pharmaceutical investments. However, given the presumed potential of genetic association studies, the databases and linked collections of samples, have themselves become a commercial commodity of enormous financial value.
13. In most science-industry partnerships, scientists contribute intellectual property, while industry provides the resources needed for clinical applicability, sales and marketing. In the case of large-scale genetic association studies, the collection services have financial value even prior to any intellectual contribution. In addition, the value of databases depends on the quality of the linked medical information, which is often the result of previous public health funding, particularly in countries with socialized medicine, such as Israel. In this setting, the single DNA sample that is donated by the individual has little financial value and is obviously not a national resource. However, when the sample is part of a large collection of samples linked to publicly funded clinical data, then the appropriate pricing for a single DNA sample has been estimated to reach \$50,000 (Bear JC, 2001). This may be considered by some as a national asset. An implication might then be that national benefit and interest should be taken into account in regulating the establishment and maintenance of such databases, either by public and/or commercial entities, as well as in regulating access to these databases.
14. Rightful allocation of benefits and profits stemming from genetic databases is complex. Biomedical research clearly stands to benefit, leading ultimately to benefits in human health. Indeed, this societal benefit is the rationale for the altruistic participation of research subjects who donate samples and allow access to their personal and medical records. However, it is a fact that in Israel the public funding allocated for such research is much below the level that would be justified in view of its societal benefit. Hence, it is more likely that much of the research will actually be performed by or on behalf of commercial pharmaceutical companies that undertake these projects with the aim of financial profit. These financial incentives mandate that the informed consent given by individual patients or donors of sample and linked medical data, should make it clear that he/she consents to financial gains by third parties.
15. There are fundamental consequence to the fact that large-scale research (and the eventual development of a drug) will most often not take place at all without commercial funding and be



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largely dependent on the direct involvement of pharmaceutical companies. A balance must, therefore, be found between the financial investment of the companies involved and the public investment, be it in the form of altruistic participation or be it the medical infrastructure without which the databases could not exist. This balance may be particularly difficult to achieve in developing countries that lack the scientific infrastructure, or in small countries like Israel where Biotechnology companies do not yet have the scope to master worldwide markets. The commercial entities involved are likely to seek partnerships abroad or be owned by multinational or foreign corporations, and thus a large proportion of the profits is likely to be enjoyed elsewhere. It would be especially disturbing if the resultant drugs are beyond the means of the research subjects and/or the health system that made the research possible. Finding a mutual benefit in the foreseeable future is therefore essential in order to justify public participation in research on the one hand and commercial investment on the other.

Large-scale genetic databases need guidance at the National level

16. Considerable organization and financial means are required for assembling large scale collections of DNA samples and deriving databases of genetic information linked to health records of individuals. The magnitude of the operation together with the specific ethical issues mentioned above - particularly regarding commercial initiatives - underscore the need for national guidance. Clearly there should be nationwide moral (if not financial) support for such projects.
17. Different countries have chosen different ways to develop this research, with some countries opting to exploit it as a National project (see Appendix on "Large-scale DNA Collections in the World"). One example is Iceland, where an exclusive relationship was developed between controllers of the database and a single commercial company. The Iceland deCODE database makes use of extensive state genealogical and health records, and consent to participate was implicit rather than active. In Sweden a collection established with public funding is being commercialized through contract research on behalf of pharmaceutical companies. In other countries (e.g. Estonia), databases are established by the government and publicly owned, but are maintained by commercial funding from companies that pay for access to the database. In addition, a number of commercial companies already own established DNA collections, although these are usually smaller than national databases.
18. A different approach has been chosen in the United Kingdom where a non-profit national organization, the Wellcome-Trust Fund working with the Medical Research Council, plans to establish Biobank UK, a genetic database of 500,000 people. In May 2002, the UK Human Genetics Commission has issued a comprehensive bioethical report: "Balancing interests in the use of personal genetic data" shedding light on the guiding principles for this initiative. In the section on particular issues of "Research databases and DNA collections"¹, the report addresses two concerns - one relating to the privatization of genetic resources, and the other to governments that consider such databases as a valuable national resource from which benefits may be obtained. The report proposes to restrict this latter notion and to rather state "that large-scale population genetic databases established by public funding are a national asset: this means that national benefits and interest should be taken into account in determining the terms upon

¹Pages 101-106 of the UK report. Available upon request from the Dr Yossi Segal, Israel National Academy of Sciences and Humanities.



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which access is to be granted to such databases”. The report further proposes “independent oversight and compliance monitoring” and recommends that “the governance of genetic research databases and DNA collections should allow for oversight by an independent body – whether it is an ethics committee or another body – which is separate from the owners and users of the database.”

Perspective for Israel

19. The Bioethics Advisory Committee of the Israel Academy of Sciences and Humanities has, during the year 2002, delineated the ethical issues pertaining to population-based large-scale genetic collections and databases in the State of Israel, bearing in mind the unique characteristics of this country and its peoples. This task was undertaken in the light of debates at the Ministry of Health (for example in the National Helsinki Committee on Genetic Research in Humans), in the Knesset and in the Israel Medical Association (Ethics Bureau²), following the initiation of the first large-scale DNA collection for genetic association research by an Israeli commercial company (IdGene). The deliberations of the Israel Academy Bioethics Committee were aimed at defining a broader set of principles, dealing in parallel with both public and commercial DNA collections and genetic databases. This report reflects the deliberations and proposes detailed guidelines for the implementation of this important new field of genetic association research.

² A document on recommendations for genetic research in large populations has been prepared by the Israel Medical Association, Ethics Office (chaired by Prof. Avinoam Reches). Many recommendations are common to those in the present report.



Chapter 2: Premises for the Guidelines

A. Nature Of Large-Scale Genetic Collections And Databases For Medical Research

20. It is recognized that there is a need for establishing large-scale, population-based, collections of DNA (or of human biological material that contain genetically informative macromolecules, such as RNA and proteins) that will be used for **medical research** with the aim of establishing **associations** between genes and diseases, including psychiatric diseases. These novel genome-wide association genetic analyses will be particularly useful to identify genes involved in many common pathological conditions, which are multigenic/ multifactorial in origin (e.g. cardiovascular diseases, diabetes, asthma, schizophrenia, etc.). In view of its enormous promise for medicine, this research should be encouraged and supported, while also being cognizant of the ethical issues involved. It is the purpose of the proposed bioethical guidelines to allow the research to proceed for the sake of human welfare and in full respect of Human Rights and Human Dignity.
21. It is recognized that it will be necessary to collect and store large numbers of **genetic samples** for this research (from 10,000 to 100,000 or more samples). The molecular analyses of the samples will serve to establish **genetic databases** containing genotyping information, including genetic polymorphisms of the populations studied. The databases of genetic information will have to be linked to databases of medical information on the individual donors of the samples. Continuous access to health records and clinical data linked to the samples is often of critical importance for this type of genetic research, which aims to find significant association between genetic differences and well-defined human diseases. This raises challenges related to the privacy and confidentiality of the medical records and other information of the patients as well as of the healthy controls who may be involved in the studies. These issues differ from those of the usual family-based or small-scale existing collections.
22. It is recognized that genetic association studies are often (although not necessarily) carried out in cohorts of patients and healthy controls belonging to a single ethnic group, so as to make the population homogenous in most respects except for the particular disease studied. In consequence, ethical issues may be raised pertaining to the protection of the rights of the groups and populations involved, particularly in terms of potential stigmatization or discrimination of a whole ethnic collective. There may be additional fears of misuse of the genetic information against the group; for example, attempts to identify genetic profiles of vulnerability to harmful agents.
23. It is to note that such DNA collections may be used for other research aims, which are not strictly medical but fall in the scientific category of human sciences, including non-pathological behavioral genetics, historical studies on population migrations or sociological studies. From the bioethical point of view, such other applications should be considered as separate and distinct from the medical genetic research, which is the topic of this document. Consent to donate DNA for medical population genetic studies does not include use of the samples or the databases for other purposes. Any application that does not state the aim of alleviating human suffering must be subject to even more stringent ethical control than the medical applications.



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In addition, the databases produced for medical research should not be utilized for police or judiciary motives, although exceptions might be necessary for emergency public security situations, e.g., identification in mass-casualties.

24. It is essential to reiterate, as stated by the Human Genome Organization (HUGO), “the importance of recognizing that the pursuit of scientific knowledge is essential to human progress and to the relief of human suffering. This pursuit must adhere to international norms of Human Rights.” The special nature of DNA and genetic information with respects to individual rights has been recognized in the Law on Genetic Information, adopted in Israel in 2000. Handling such information from large populations, especially when linked to individual’s medical information, makes it imperative to have ethical guidelines for the collection of DNA samples as well as for handling the ensuing genetic/medical databases. Finally, interpretation of the results of such genetic research must adhere to the strictest principles of intellectual honesty, emphasizing that the central notion is one of genetic predisposition, rather than of determinism, and taking into account the interactions of genes and environment.

B. Public Versus Commercial Collections And Databases

25. Large-scale DNA collections and genetic/medical databases require considerable organizational and financial means. Ideally, **publicly funded** DNA collections and genetic databases could be set up as a common resource for medical research in Israel. The public funding could include financial support from government and research granting funds in Israel, as well as philanthropic or charity funding.
26. Establishing in Israel one or several public collections of DNA samples to carry out the genetic medical research indicated above, would be justified for several reasons:
 - (1) It would preserve the freedom of access to the genetic information on Israeli populations.
 - (2) Since the scientific and commercial value of DNA collections depends intrinsically on the accuracy of the linked medical information, and since this accurate medical information exists thanks to long-term public funding in the Israeli health system, a public collection would preserve this existing public investment.
 - (3) It would permit and support the work of independent researchers in medical human genetics.
 - (4) It would enhance public and societal awareness of the various benefits that might result from the research.
27. In the absence of such public collection and database, the most likely alternative is that the critical genotyping information will be available only to those private commercial companies that will invest in this research. The genetic research might then possibly (although not necessarily) be restricted to those therapeutic or diagnostic aims suited for commercial interest. It is, therefore, considered of public interest that medical genetic research be allowed to proceed by independent researchers as well, and in as large a scope as possible, taking into account the serendipity of scientific and medical discoveries.
28. However, it is a fact that public funding for research, particularly in Israel, is far from the level required for the immense task of identifying the association between genes and multifactorial



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diseases. It is also a fact that Commercial Companies often represent an efficient tool for the advancement of therapeutics, pharmaceuticals and diagnostics.

29. In consequence, the initiative of **privately funded Commercial Companies** to carry out medical research on large-scale collections of genetic samples should not be prevented nor impaired *a priori*, provided that they adhere to the established bioethical regulations and compliance monitoring system.
30. The principle proposed for Israel, therefore, is that there should be no monopoly on the large-scale population based genetic research, either public or commercial. Rather, there should be mutuality between the public and commercial aims of large-scale genetic databases, a principle that is easy to state but difficult to translate into practical measures. Thus, it is important that private initiatives be perceived as bringing benefits to medical knowledge and human well-being in general rather than being solely aimed at commercial gains. The voluntary nature of the individual participation in genetic research must be respected without blurring the lines between public research and commercial enterprises, in order to prevent the public from losing faith in the promises of medical research. The following guidelines will, therefore, address both public and commercial large-scale collections of DNA samples, indicating in each case the specific recommendations for ethical performance of this type of genetic medical research.

C. Need For A Statutory Authority For Genetic Collections And Databases

31. In some countries, the State is directly involved in the collection of genetic samples or in the commercialization of genetic collections and databases (see Appendix on large-scale DNA collections in the World). However, such direct State involvement is problematic and Israel should refrain from it. In fact, State involvement poses serious questions regarding the principle set out in the Universal Declaration on the Human Genome and Human Rights (Article 1), namely, that the human genome is “a heritage of mankind”. From this principle, it follows that genetic information should not be considered as owned by a particular State to be handled as a national resource or property, or used by the State for its own purpose.
32. It follows, therefore, that the State of Israel should not have direct control or direct commercial interest in managing a collection of its population’s DNA or the derived databases as a national resource. Notwithstanding, these may be viewed as an asset from which the population should benefit. Coherent with this view, there is a need to ensure that the planned genetic research will enrich the public-domain medical knowledge, benefit the public health-care and be carried out with respect of ethics and human rights.
33. Therefore, it is proposed that large-scale genetic collections and databases be overseen by an independent public body, which will *not* be the State. In particular, it is proposed to create for this purpose a **Public Statutory Authority** designated as the:

“Human Genetic Israeli Collection Authority” or HUGIC Authority.

(רשות לאוספים של דגימות ומידע גנטי של אוכלוסיות בישראל)



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34. The HUGIC Authority will have administrative power to enforce the bioethical guidelines and the policies for monitoring the establishment, management and uses of large-scale, population-based, genetic collections and the databases of derived genetic/medical information. The same statutory authority will further monitor the research carried out by authorized commercial companies and enforce policies to ensure their compliance with the bioethical guidelines. These guidelines will be those adopted at the level of the national Bioethics committees, in consultation with appropriate bodies and as outlined in the present document.
35. One aim in establishing the HUGIC Authority is to have an entity specialized in all aspects of large-scale population based DNA banks and genetic databases. According to the present administrative situation in Israel, it is the mandate of the “National Helsinki Committee for Genetic Research in Humans” to perform case-by-case professional ethical evaluation of individual research proposals. The Helsinki Committee will follow the principles and guidelines adopted and consult with the HUGIC Authority on any issue of ethical significance that may arise about a particular research proposal in the field of population- based genetic research, prior to approval. In order to ensure integration of the work, there will be a partly overlapping membership in the HUGIC Authority and in the Helsinki Committee.
36. The HUGIC Authority will be a non-profit organization but, if needed, will employ a Technology Transfer Office (TTO) for its financial and commercial transactions. Such a TTO will be an **at arms-length** organization according to the common practice of universities in Israel. In this way the Authority will preserve its moral status but be able to cope in an ethical manner with the inevitable practical implications of modern human genetic research.
37. The Authority will thus be able to receive grants from philanthropic funds as well as from government in order to establish a Public collection of genetic samples.

Composition of the Human Genetic Israeli Collection (HUGIC) Authority :

38. The Authority will be appointed by the Israeli government through its “Ministerial Subcommittee for Science and Technology”.
39. The composition of the HUGIC Authority will be interdisciplinary (scientists, ethicists, lawyers) and should include four members of national Bioethics bodies and three members from the National Helsinki Committee for Genetic Research in Humans. There should also be representatives of the Ministries of Health and of Science. An operation officer should be appointed to supervise and direct the TTO conducting the eventual commercial transactions on the DNA collections or on the genetic databases derived from them.



Chapter 3: Detailed Guidelines

Section I: Establishment Of Population-Based Large-Scale Dna Collections

All procedures in this and following sections will be in keeping with the Israel Genetic Information Law, 5761-2000.

A. Organization authorized to perform a Collection:

40. Public Collections:

- a) A mandate of the Human Genetic Israeli Collection (HUGIC) Authority will be to make all efforts to secure public financing toward the establishment of a Public collection of DNA samples for the purpose of Medical Research, in particular for identifying genes involved in the etiology of multigenic / multifactorial diseases.
- b) The type of DNA Collection to be established and the research performed on it will be for projects that were reviewed and authorized by the National Helsinki Committee for Genetic Research in Humans through established procedures (see Section IV) and with the approval of the HUGIC Authority.
- c) The HUGIC Authority will issue a Call-for-Proposals. The proposals will be evaluated through a peer review process in order to select one or more medical center (or hospital or health maintenance organization (HMO/Kupat Holim), preferably affiliated with an Academic Institution (or other Public Institution) to perform the collection of DNA samples and the research.
- d) The academic (or public) institution, or the medical center (or hospital) issuing the proposal may have its own Technology Transfer Office, as usual in Israeli Universities. Prior to appointing it for establishing or operating a DNA collection, an agreement will be necessary which will give all rights to the HUGIC Authority.
- e) The medical center will appoint Research Physicians, **who should not be the physicians in charge of treating the patients** from whom DNA samples will be collected. The Research Physicians will obtain authorization from each treating physician to access the medical file of his/her patients provided that these have given informed consent to donate DNA samples for this type of research (for the Informed Consent process, see Section IV).

41. Commercial Collections

- a) Israeli biotechnology or pharmaceutical commercial companies will be entitled to propose the establishment of a DNA Collection for the purpose of medical research, in particular for identifying genes involved in the etiology of multigenic / multifactorial diseases.
- b) The type of DNA collection and the research performed on it will be for projects reviewed and authorized by the National Helsinki Committee for Genetic Research in Humans through established procedures (see Section IV) and with the approval of the HUGIC Authority.
- c) The authorized Company will call on one or more medical centers, hospitals or other health institutions (such as HMO/Kupat Holim) to appoint individual physicians or teams to collaborate in the collection and in the research with the commercial company. The company will not directly approach the individual physicians. These arrangements should be specified in the application.



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d) In this case as well, the appointed “collaborating Research Physicians” **should not be the physicians in charge of treating the patients donating DNA samples**. The collaborating physicians will obtain authorization from each treating physician to access the medical file of his/her patients providing these have given informed consent to donate DNA for this type of research (see Section IV). Informed consent under such conditions should include a statement that the patients are aware of the fact that the research will be performed within the framework of a commercial body.

B. What is being collected:

42. **Public Collections**

- a) DNA samples (from blood samples or any other source including pathology slides or biopsies, or archived samples)
- b) Medical information on the patients/donors, which will be solely that information related to the genetic disease on which the authorized research is being conducted. This information may be broader than genetics and include medical information that may also pertain to family members. The type of information collected for healthy donors (as opposed to patients) should be as limited as possible.
- c) Information pertaining to the ethnic origin of patients/donors, mostly as self-reported.

43. **Commercial Collections**

- a) DNA samples (from blood samples or any other source including pathology slides or biopsies)
- b) Medical information on the patients/donors, which will be solely that information related to the genetic disease on which the authorized research is being conducted. This information may be broader than genetics and include medical information that may also pertain to family members. The type of information collected for healthy donors (as opposed to patients) should be as limited as possible.
- c) In commercial collections, however, the information collected will be limited to the specified groups of patients and healthy donors which have been defined as the aims of the authorized research. Hence, the scope of any collection, or consortium of collections, should not represent a significant part of the whole spectrum of the Israel population.

C. Financing of the Collection and the Research

44. **Public Collections**

- a) Public grants provided by government, by a public association, or funds collected from the Public (“March of Dimes” or Telethon type) may be used.
- b) Private funding from benefactors, non-profit charitable funds may also be used.

45. **Commercial Collections**

The authorized commercial company will finance the collection and the research.

D. Payments to Researchers: compensation for services



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46. Public Collections

- a) The academic (public) institution that was selected to establish the DNA collection and perform the research will be reimbursed for the expenses, as usually practiced for scientific research financed through public grants.
- b) The grant should cover total costs to the hospital/medical center/HMO, including both the labor costs of the participating physicians and the laboratory expenses. It will be permissible to provide incentive for the collection and the research (e.g., as overhead).
- c) The Institution will be responsible for ensuring the collaboration of the participating Research Physicians and for payments to them intended to cover their labor and expenses. It is important to stress, as an ethical principle, that physicians should not be paid for the participation of their patients in the DNA collection, but for their own medical professional collaboration.

47. Commercial Collections

- a) Medical centers, hospitals and other health institutions (e.g., HMO/Kupat Holim) participating in the collection and the research will be reimbursed for expenses as negotiated with the commercial company. The procedure will be modeled on the practice for clinical trials financed by commercial companies in academic (public) institutions.
- b) These institutions will be responsible for ensuring the collaboration of the Research Physicians who have been appointed to participate in the collection and in the research, and for payments to them intended to cover their labor and expenses. The company will not directly deal financially with individual physicians or researchers who are not their employees.
- c) In addition, the company will undertake contractually to provide reasonable returns on the eventual profits of sales of products derived from the DNA collection and the research, as indicated in Section III.

48. For both Public and Commercial Collections

The donors of DNA samples (patients and volunteers) will be informed that their donation is voluntary, without payments (except for reimbursement of eventual expenses). They will be informed that payments are made to the Institution, which in turns provides payments to participating physicians and researchers, these payments being aimed exclusively at covering their labor and expenses (see Section IV, Informed Consent).

Section II: Processing Of The Dna Collection During The Research

A. Monitoring of the Collection and of the Research

49. For both public and commercial Collections

- a) The HUGIC Authority will be responsible for the monitoring.
- b) All steps of the collection and the research will be monitored and reports will be issued at predetermined time periods to describe the activities performed and the progress.
- c) Deviations from the authorized procedures for collection of samples, processing of samples, research project or forms of commercialization can be sanctioned, including by annulment of the authorization given.



B. Access to the DNA samples and the Medical Records

50. Public Collections

- a) Any independent researcher (not employee or contractor of a commercial company) can apply for access to the Public collection of DNA samples.
- b) The application will be evaluated by a peer review process conducted under the responsibility of the HUGIC Authority. If selected, the application will in addition require the usual approval of aims and methodology by the National Helsinki Committee for Genetic Research in Humans.
- c) A commercial company can apply for use of the Public DNA collection under financial terms to be negotiated with the TTO of the HUGIC Authority (see Section III), terms to be approved by the HUGIC Authority.
- d) If such license to use the Public collection is given, the commercial company will in addition require the usual approval of aims and methodology by the National Helsinki Committee for Genetic Research in Humans.
- e) Access to the medical records of the patients/donors of DNA samples will, in all cases, be exclusively performed through the authorized research physicians who were appointed to establish the Public collection of DNA samples (see Section I, paragraph 40, e).
- f) The medical records will be coded so that researchers receive DNA samples that are linked to the medical information in a completely anonymous way.
- g) In case of public emergency, the government may by appropriate decree have access to the decoded database for purposes justified by the emergency (e.g. identification in mass casualties), but excluding forensic investigations.

51. Commercial Collections

- a) The Israeli commercial company is granted exclusive rights to access the DNA collection provided that it has initiated and financed it fully. These rights will be limited for a pre-determined period of time, dependent on the diligence and progress in the project. After this time the collection will be made public under the responsibility of the HUGIC Authority.
- b) In addition, independent researchers should be allowed to purchase access to samples and medical information at costs that will be set by the Director-General of the Ministry of Health, and provided that their work is not in conflict of interests with the aims for which the commercial company received authorization to establish the collection.
- c) Access to the medical records of the patients/donors of DNA samples will be in all cases be exclusively through the physicians appointed to collaborate with the commercial company (see Section I).
- d) The medical records will be coded so the company and its research physicians receive DNA samples that are linked to the medical information in a completely anonymous way.
- e) In exceptional cases where special public health benefits may be invoked, the HUGIC Authority may negotiate with the company for access to the DNA collection and the database.
- f) In case of public emergency, the government may by appropriate decree have access to the decoded database for purposes justified by the emergency (e.g. identification of mass casualties), but excluding forensic investigations.



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C. Access to the Genetic Database derived from the DNA Collection

52. Public Collections

Access to the genetic database generated by an academic/public institution will be as above in B paragraph 50.

53. Commercial Collections

The company that has produced the genetic database will retain exclusive access to it. However, a time limitation may be set for this exclusivity after which access to the database may be opened to independent researchers, subject to collaborative agreements with the commercial entity.

Paragraph 51, e and f apply here as well in exceptional cases.

D. Further Studies on the same DNA Samples or Genetic Database

54. For both Public and Commercial Collections

a) Any further research will be restricted to similar type of research on genetic diseases (including psychiatric diseases), and this will only require notification to the HUGIC Authority who will inform also the National Helsinki Committee.

b) Uses of the collection for other research purposes than genetic diseases, such as non-pathological behavioral genetics, historical and population migration studies, or others, will require a completely new application and be subject to authorization as a novel proposal for establishing a collection of DNA samples.

c) Neither the HUGIC Authority nor the National Helsinki Committee will have a mandate to authorize usage of the collections for non-scientific purposes, such as for police forensic investigations.

E. Exporting of the DNA Samples or of the Genetic Database

55. Public Collections

a) Exporting the Public DNA sample collection from Israel will in principle *not be permitted*. Exceptions may occur solely with explicit authorization by the HUGIC Authority, which will consult on this matter with appropriate authorities and bodies. For example, it may be decided to negotiate deals with a multinational or foreign company in order to develop specific research projects and/or products. The precise nature of the medical information on the patients/donors that will be released will have to be decided specifically.

b) As to the genetic database, export from Israel will only be permitted if authorized by the HUGIC Authority, and only in those cases where such export will be deemed essential for commercialization by a multinational or foreign company. A criterion will be whether this is beneficial for human health and well-being, and will assist the Israeli Health system.

c) Any such deal involving export will always be subject to the regulations of the Israeli Ministry of Industry and Trade, and other bodies for international commercial transactions.

d) Export should not be allowed if the samples or database are representative of the entire spectrum of the Israeli population (in the spirit of Section I, B, paragraph 43, c.).

e) The option of export should be stated in the informed consent form signed by the donors/patients.



56. Commercial Collections

- a) Exporting of a commercial DNA sample collection will not be permitted. The Israeli company that has received authorization to create the DNA collection will not be allowed to export it from Israel and should exploit it in its Israeli facilities. Nevertheless, the HUGIC Authority will have the power to make exceptions. One such exception may be the case of a local Israeli company being a subsidiary of a multinational corporation that has undertaken contractually with the State of Israel not to infringe on the rights and public security requirements of Israel. Transfer within the corporation may then be opened to authorization.
- b) Exporting of a commercial genetic database derived by the company authorized to perform the collection and the research will only be permitted if duly and explicitly authorized by the HUGIC Authority. A relevant criterion in the decision will be whether this is beneficial for human health and well-being, and will assist Israeli patients.
- c) Any such deal involving export will always be subject to the regulations of the Israeli Ministry of Industry and Trade, and other bodies for international commercial transactions.
- d) Export should not be allowed if the samples or database could represent the whole spectrum of the Israeli population (in the spirit of Section I, B, paragraph 43, c).
- e) The option of export should be mentioned in the informed consent form signed by the donors/patients.

Section III: Forms Of Commercialization For Genetic Data From Population-Based Large-Scale Dna Collections

A. What is commercialized?

57. Public Collections:

- a) Although the primary aim of the Public collection is to support independent medical and scientific research, this aim does not exclude commercialization, subject to limits as follows:
- b) Only the genetic database derived from the analysis of the Public collection of DNA Samples will be subject to commercialization by establishment of transactions with commercial entities.
- c) The HUGIC Authority will be responsible for any form of commercialization, involving or not its TTO.

58. Commercial Collections:

- a) Commercialization will be restricted to specific genes for the diseases that were included in the company's declared and authorized aims, and were identified during the research.
- b) Only with special agreement by the HUGIC Authority, will the entire database be subject to commercialization and open for access by another commercial entity for a research that will have to be approved by the Authority.
- c) The DNA or tissue samples collected by a commercial company will not be sold to another commercial party. Exceptions may be granted by the HUGIC Authority and limited to transactions within a multinational corporation of which the Israeli company is a subsidiary (conditions stipulated in Section II, E, paragraph 56, a).



B. Forms of Profit from Commercialization

59. Public Collections

- a) Granting of commercial licenses to utilize the genetic database, or results of the research, will be a prerogative of the HUGIC Authority, through its Technology Transfer Office (TTO), which will act with a national perspective. The HUGIC and its TTO will retain the intellectual property and receive milestone payments or share in Royalties as negotiated with the commercial party. The HUGIC TTO will have the responsibility and power to reach in advance proper agreements with the academic/public institution (with which the Public collection is affiliated) and its TTO, to deal with issues of inventions, in particular regarding the genetic database and results derived from the collection.
- b) As a principle, the financial returns will be dedicated by the HUGIC Authority to patients/donors welfare through:
 - (1) A national fund for genetic research on human diseases.
 - (2) Providing genetic testing and medications to patients suffering from, or at high risk for genetic diseases, for example when frequent monitoring is necessary (e.g. BRCA mutations, etc..).
 - (3) Support of related research directed at finding cures to human diseases.
- c) The same rules will apply for any form of commercialization, under the exclusive responsibility of the HUGIC Authority.

60. Commercial Collections

- a) It is recognized that activities of the biotechnology and biomedical Industries indirectly benefit the State through economic boost and taxes. The investment made by the company to collect the DNA samples is also recognized.
- b) However, the special nature of the genetic samples taken from a consenting population, without appropriation of the genetic material, implies further obligations of the commercial entity to the medical welfare of the population. In addition, the value that DNA collections have for medical research depends on the linked medical information and this information is almost entirely a contribution of the publicly-funded health system.
- c) Therefore, the company will be asked to provide a reasonable financial return on its profits from the genetic collection in the form of contributions for relevant research work in the medical centers participating in the sample collections, research being aimed to benefit the patients/donors welfare.
- d) In addition, the company that has profited from a genetic collection taken from a large segment of the Israeli population, will be asked to provide special conditions allowing Israeli patients to benefit from drugs and/or of diagnostic clinical tests that were developed based on the genetic samples collected. This is in line with what is practiced today by companies carrying out clinical trials in regard to patients who participate in the trials.



C. Ownership of the DNA Collection itself:

61. Public Collections

a) Considering the ethical concept that the model of property does not apply to the human body or its parts, the Society is no sense “owner “ of the DNA of its individual members. Every individual has full rights on his/her own DNA. However, the informed consent form signed by each donor/patient stipulates that he/she has out of free will transferred all appropriate rights on the usage of the DNA sample for establishment of the Public collection and for its purposes.

b) The HUGIC Authority will be the body entitled to retain these rights, in order to guarantee a coherent national policy. In particular, these rights allow it to derive a genetic database, which will be the basis for conducting financial and commercial transactions through the for-profit TTO, as indicated above.

62. Commercial Collections

a) The Company cannot be the “owner” of the DNA samples, but will operate according to the informed consent (see Section IV, B) given by each donor/patient granting the Company rights for the usage of the samples in order to perform the research as stipulated in the present guidelines. The donor/patient grants permission without financial payment; in return for donation of the samples is the promise of medical welfare for the community and special conditions under which diagnostic tests or eventually therapies will be made available to the community.

b) Hence, the company will not be considered as holding rights to sell or commercialize the DNA samples themselves.

D. Ownership of the Genetic Database derived from the DNA Collection:

63. Public Collections

a) The academic (public) institution that derived the database from the DNA collection will have the rights on the database, but its licensing and commercialization will be the responsibility of the TTO of the HUGIC Authority. This falls under the provisions of any agreement made with the TTO of the academic (public) institutions (Section III, B, paragraph 59, a).

b) The HUGIC Authority controlling the functioning of the collection will retain the power to allow other academic (public) institutions to share the database for authorized research projects. In this case, this will be preceded by negotiation of agreements between the second institution and the TTO of the HUGIC Authority.

64. Commercial Collections

a) The company has the commercial rights on the database but is allowed only to commercialize specific genes or derived tests and therapies, but not the entire database unless explicitly authorized to do so by the HUGIC Authority.

b) The company will undertake to grant academic researchers access to the database, provided that this is part of a collaborative agreement between the researchers and the company.

E. Ending the Activity of the DNA Collection



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65. **Public Collections**

- a) Should the activity on a Public collection be terminated, the DNA samples will be returned by the institution, transferred to a proper deposit place and will remain under the control of the HUGIC Authority.
- b) The Genetic Database will remain publicly accessible (as in Section II, A), provided that any research conducted on it is under conditions where the genetic information is anonymous.

66. **Commercial Collections**

- a) In the event that the commercial company (that was authorized to perform the collection and the research) is closed or sold to a third party, the DNA samples as well as the genetic database will be immediately transferred to the HUGIC Authority, which will have all the rights on these, as stipulated for public collections.
- b) This condition should be included in the agreement signed by the commercial companies that want to create private DNA Collections, as a pre-requisite to approval by the HUGIC Authority. The clause detailing these conditions, meant to prevent companies from making the collection with the intention of later being bought by a foreign or multinational company, should specifically state that this condition will be an inseparable part of any due diligence and/or of its intellectual and material properties.



Section IV: Consents And Protection Of Individual Rights And Public Interests

A. Steps to be taken before establishment of a DNA collection

67. For both Public and Commercial Collections

a) The establishment of a new DNA collection should be preceded by a declaration of the aims of the research to the HUGIC Authority, which will take the proper steps to ensure that an appropriate body will explain the importance and scientific value of the research to the participants. When deemed necessary, a **consultation** involving the public at large or specialized sectors will be carried out to explore ways of assuring protection of individual and public interests during and following the research on the population-based DNA collection.

b) A detailed comprehensive **Research Application** will be submitted to the National Helsinki Committee for Genetic Research in Humans, with simultaneous notification to the HUGIC Authority. The total number of samples and all the participant centers or individual physicians providing samples, will be stated. In addition to the usual contents of a Helsinki Application, the following will be detailed:

- (1) Principals and secondary aims of the research (diseases studied or genes searched)
- (2) Methodology of the genetic analysis, of sample storage and database storage.
- (3) Benefit expected for the patients and other donors of DNA samples
- (4) Ethnic or other socially-defined group(s) involved in the study
- (5) Time-frame allotted to keep the DNA collection and to perform the analysis
- (6) Any links between this and other submitted projects, to ensure that the application is comprehensive and includes all the patients and donors involved in the collection.
- (7) How the Genetic Information Law will be adhered to in this study: anonymization of samples, coding of the medical information attached to the samples, confidentiality.
- (8) Presentation of the informed consent form and explanatory notice including proper disclosure of the functions of physicians and researchers involved.

B. Informed Consent Process for donors of DNA samples

68. For both Public and Commercial Collections

In addition to the usual informed consent procedure, the physicians participating in the research will inform every subject donating a DNA sample of the following, which will be included in the Informed Consent Form:

69. (1) Purpose and impact of the research:

- a) Each patient/donor will be informed that he/she will continue to be treated by the available therapies, whether he/she consents or does not consent to participate in the research
- b) That the research for which the DNA samples are being collected may not immediately be related to the treatment of the disease of the donor.



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- c) That while the patient/donor may not benefit directly from the Research, it is expected that there will be clear benefits for the community of patients and for the future, particularly with respects to patients suffering from the same disease.
- d) That those conducting the Research do not necessarily intend to inform the donor of the samples of the specific results obtained from testing their individual sample.
- e) The researchers, through the offices of the participating physicians, will undertake the responsibility to inform the participants in the study of clinically-relevant results,. Participants will eventually be offered testing for mutations or polymorphisms in the gene(s) discovered.
- f) The overall results of the research project will be communicated through appropriate and ethical scientific publications, as well as by means of popular scientific mass media.

70. (2) Subsequent research on the same samples:

- a) The patient/donor will be informed of the possibility that additional research could be performed on the same samples, which will be described as explicitly as possible.
- b) That such additional research will be subject to the regulations set in Section II, D.
- c) That future research may be conducted within the framework of a commercial company that may become associated to the research.

71. (3) Anonymity of the DNA samples:

- a) The patients/donors will be informed that the collection is anonymized (non-identified samples or coded samples linked to medical information), and that the participating physicians may have repeated access to the medical file of the donor. Only the participating physicians have the code, which may allow them to inform the patients/ donors of clinically relevant results [as above in paragraph 69, e].
- b) The patients/donors will be informed that measures are being taken to prevent risks pertaining to the ethnic or other socially-defined group from which the collection is established.

(4) Financial aspects of the Research:

72. **For Public Collections**

- a) The patient/donor will be informed that the HUGIC Authority can grant access to the anonymized DNA sample collection or to the genetic database to private commercial companies against financial gains, it being understood that these will generally benefit the health system.
- b) The patient/donor will be informed that the medical centers will be paid for their participation and services and that participating physicians will be paid for their labor and expenses.
- c) The patient/donor agrees to transfer rights on the DNA sample to the Public collection, and he/she will not be directly paid, except for expenses reimbursement.

73. **For Commercial Collections**

- a) The patient/donor will be informed that the research is conducted by a commercial company.
- b) The physician will explicitly inform the donor in the event that the physician receives payment for labor and expenses, and that the medical centers and other parties receive financial gains from the research.



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c) The patient/donor will grant to the company permission to use his/her DNA sample, agreeing that he/she will not be directly paid, except for expenses reimbursement.

In all cases the Informed Consent Form will be presented in a way that allows the donor to state:
☐: I agree
☐: I disagree.

C. Guaranties against Risk of Stigmatisation

74. For both Public and Commercial Collections

a) In order to avoid statements that may lead to stigmatization, the HUGIC Authority will distribute instructions to all researchers pertaining to the need for extreme caution when writing articles and communications that may have implications for the whole ethnic or otherwise socially-defined group. The participants will have to sign that they accept to avoid and prevent any stigmatization. Sanctions will be applied if these rules are not followed.

b) Efforts will be made toward educating the media and the public on the notion that no “ideal genome” exists, that all individuals carry some deficiency genes and that ethnic groups may statistically have different distributions of such genetic characteristics. No group can be stigmatized because all carry particular gene distributions.

D. Guaranties against Hostile Uses

75. For both Public and Commercial Collections

The application for establishment of a human genetic sample collection will have to describe the procedures aimed at protecting access to the samples and to the derived genetic database so that “genetic profiling” of an ethnic group cannot be used by hostile elements in attempts to harm the group. Security measures may be required to avoid the information falling into the hands of hostile and terrorist organizations.

E. Protection of free Research in Human Genetics

76. For Public Collections

In order to prevent jeopardy to free scientific research and unfair use of patients and donors, all scientists can apply to participate in research projects utilizing the Public DNA sample collection.

77. For Commercial Collections

a) In order to prevent jeopardy to free scientific research and unfair use of patients and donors, the company undertakes to be open to collaborations with outside scientists. These collaborations should be negotiated with the commercial company, which should declare its openness to support such collaborations provided they are not in direct competition with the aims of the research that the company was authorized to perform.

b) Another way by which the company is invited to contribute to free research is through reinvesting a part of the profits eventually derived from the collection to support of research in the participating medical centers and academic institutions.



Appendix: Large Scale Dna Collections And Genetic Databases In The World

78. The issue of large-scale, population based DNA collections has become a subject of world-wide discussion, and several international organizations (including the World Health Organization [WHO] and the World Medical Association) are in the process of formulating appropriate guidelines. This is a result of a number of scientific, commercial and political developments in recent years, some of which are summarized here and in the list of references.

Commercially established large-scale DNA collections

79. **The Iceland experience:** (excerpts quoted from Annas G, *New England Journal of Medicine* 2000; 342:1830-3)
Research on genetic variation aims to understand how genes function and requires the comparison of DNA samples from groups of individuals to identify variations that might have importance for health or disease. This work is easier if the samples are linked to accurate medical records and genealogical information. Iceland has medical records for all its citizens going back to World War I and detailed genealogical information going back even further. Because Iceland's small population (270,000) has long been isolated and homogeneous, it is thought by many to be an ideal place to search for disease-related genes. Journalists have cavalierly labeled Iceland's "the most homogeneous population on earth" and have described the country as an "island so inbred that it is a happy genetic hunting ground."
80. In December 1998, at the instigation of a for-profit U.S. corporation, deCODE genetics, and its chief executive officer, Kári Stefánsson, Iceland's parliament passed the Health Sector Database Act, which authorized the minister of health to grant an exclusive license to a for-profit corporation to create a database of the medical records of all Icelandic citizens. The government of Iceland can use the database for planning and policy purposes, but the licensee has control over access to the data base for commercial purposes for 12 years. In return, DeCode will provide Iceland free of charges whatever drugs are ultimately developed. Individually identifiable data may not be disclosed, and confidentiality is protected by a variety of methods, including penalties of up to three years in prison for violations. A Data Protection Commission receives medical records from physicians and hospitals and codes and encrypts them before giving them to the licensee. Similar projects are ongoing or under active discussion in the United States, the United Kingdom, Sweden, and Estonia, and many others are likely to follow. Thus, the Icelandic experience may provide lessons and guidance.
81. Early in 2000, the Icelandic minister of health granted the database license to Íslensk erfðagreining, a wholly owned Icelandic subsidiary of deCODE. Opposition to the project has arisen and includes the Iceland Medical Association. Dissent seems to be fueled primarily by a belief that participation in the database has been foisted on the citizens without time for proper debate, that measures to protect privacy are inadequate for a for-profit venture, that academic researchers will not have proper access to the data, and that individual consent should be required before medical records are included in the data base.



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One of the main points of contention has been that medical records will be included in the data bank unless a person "opts out" of the system by notifying his or her physician. Research on humans requires consent, but research on data from medical records that cannot be linked to individual patients has often been considered an exception to this general rule. Nonetheless, because of the commercial nature of the data bank and its for-profit research agenda, many observers believe that individual consent should have been required. Moreover, if deCODE is correct in asserting that it has the overwhelming support of the population, obtaining individual informed consent should not have been difficult. Creating an "opt-out" alternative was not well justified by deCODE; this option cannot be exercised by children or incompetent people, and it provided those who are opposed to the plan with a focus for their criticism. By May 2000, it had been reported that more than 18,000 Icelanders (more than 10 percent of the adult population) had opted out of the research plan. A lawsuit to challenge the entire statute is also being planned by an organization formed just to fight deCODE's project, the Association of Icelanders for Ethics in Science and Medicine (Mannvernd). Thus, deCODE was right to warn prospective investors, in the stock registration form submitted to the Securities and Exchange Commission in March 2000, that "ethical and privacy concerns may limit our ability to develop . . . and may lead to litigation against us or the Icelandic government."

82. The primary purpose of deCODE is to collect and analyze DNA samples for commercial purposes. It is therefore surprising that nothing in the Icelandic statute specifically authorizes this activity or describes how it is to be accomplished. Because of this omission, the issues of community consultation and benefit and individual consent and benefit for research on genetic variation have yet to be dealt with in any detail in Iceland."

Commercializing DNA collection established with public funding.

83. Canada, Quebec: - Galileo Genomics

Founder populations are ideally suited for genetic studies because of a relatively homogenous genetic background, which reduces the overall number of disease genes segregating in the population and hence increases the relative risk of these genes in the population. In addition, young founder populations are expected to have greater linkage disequilibrium around shared identical-by-descent (IBD) genes thereby making their identification relatively cost effective due to fewer markers being required. The Quebec founder population is probably the largest and one of the best founder populations in the world for complex trait gene discovery. There are 6 million people of French origin derived from approximately 2,500 effective founders who contributed up to 80 percent of the gene pool in the Quebec founder population..

84. USA: the Framingham example

Framingham Genomic Medicine (FGM), was a genomics company created in 2000 to perform single nucleotide polymorphism (SNP)-based studies using DNA and clinical data from the Framingham Heart Study. This study, which began in 1948 has become famous as a groundbreaking long-term effort to collect detailed health information about thousands of people. Gathering medical data about residents of Framingham, Mass., over 2 generations, the study has produced a wealth of significant medical findings on cardiovascular disease. FGM was to have digitized the entire database, which includes many paper-based items such as



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X-rays, photos etc. The Framingham study is administered by researchers at Boston University, and funded by the National Institutes of Health (NHBLI), which gave more than \$40 million to the study over the years. FGM raised over \$21 million in venture capital and Boston University was to own about 20% of the company's stock (through an equity investment). FGM also agreed to fund an ethics advisory board and a science education program in Framingham schools. Through a separate fund for the city, the community would further benefit from the creation of FGM. However, ethical opposition to commercialization of a publicly funded study (mainly by the NIH) resulted in dissolution of FGM in Jan. 2001. The major issues were that a private company would profit from a publicly funded study, and that changing the open and collaborative nature of the study would allow external researchers access to both data and DNA samples. FGM planned to continue to make the clinical data accessible, while having exclusive rights to market the genetic information for a period of time that ultimately was not determined.

85. Sweden:

UmanGenomics has access to a 15 years old prospective population-based Biobank, collected from the relatively homogenous population of Västerbotten in Sweden. The Biobank contains DNA, plasma samples, and biochemical and lifestyle data from more than 66,000 individuals. The Biobank is linked to high quality disease registers, and today a substantial number of well characterized cases of common diseases like diabetes, myocardial infarction, stroke and prostate cancer are available. Samples from diseased can be perfectly matched with control samples collected under identical conditions. Furthermore, data on subphenotypes of diseases, including glucose tolerance, blood lipid levels, blood pressure etc. has already been determined for all 66,000 individuals, and additional biochemical markers can be analyzed in the plasma samples. This allows for the association of less genetically complex phenotypes to genetic variation. UmanGenomics' resources are ideally suited for association studies of common diseases. UmanGenomics AB was founded in 1999 in order to commercialize the large and population-based Medical Biobank in Umeå. This Biobank, established by a group of scientists, is a potentially important resource for industrial research. The business plan for UmanGenomics is to carry out contract research on behalf of pharmaceutical companies.

Commercial investment in a publicly owned DNA collection:

86. Estonia (Feb 2001).

Estonia decided to create its own population DNA collection as a means of attracting investments and creating a biotechnology industry which will finance health and research costs. It touts the diversity of its 1.4 million inhabitants as an advantage for analyzing complex disease (as opposed to the more common view that isolated populations are preferable). For this project, the Estonian parliament has created two entities: the nonprofit Eesti Geenikeskus (the Estonian Genome Center Foundation) and the Eesti Geenivaramu (the Estonian Genebank Foundation) - the engine of the venture. Eesti Geenivaramu (for profit) will carry out the project; Eesti Geenikeskus (non-profit) will own the data.

The project enjoys enormous popular support. A poll indicates 90 percent of 1.4 million Estonians like the idea of a big project with potential benefits for themselves, and that also helps the country's fledgling biotechnology industry. Individuals may freely access their own data, otherwise strictly secret, and be notified if the project research yields treatments that



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might be beneficial. If 1 million Estonians are genotyped within 5 years, as officials predict, Estonia will own the behemoth of population genotyping projects, the only one with a database sized in terabytes.

The Estonian Genebank Foundation was officially opened in March 2001 in the city of Tartu. Kickoff money of 20 million kroons (US\$1.3 million) funds a pilot genotyping project scheduled to begin soon. But the real major funding - \$100-150 million over five years - will come from payments of nonexclusive licenses for data access and intellectual property rights to drugs and diagnostics resulting from research. Part of the Genebank foundation's mission is to sign-up international partners, chiefly research institutes and biotechnology or pharmaceutical companies.

A 10,000-patient pilot project has started without defining a specific disease to focus on, but will take advantage of patient group registries for cancer, Parkinson's disease, osteoporosis, and diabetes. Patients coming for checkups will be invited to participate (strictly on a voluntary basis) by filling out extensive health questionnaires and donating 50 ml blood samples from which DNA will be extracted.

87. **Tonga:**

This Polynesian country located 1,245 miles north-east of New Zealand is a constitutional monarchy with 108,000 inhabitants, living in close-knit, highly inbred communities. An Australian company, AutoGen, is setting up a DNA collection and mapping facility in Tonga. Tonga will own all DNA samples collected by Autogen's scientists, and will receive annual research support and royalties from any successful commercial ventures, such as new drug treatments, that emerge from the study. Participation in the DNA collection is voluntary. The agreement was signed in January 2001, but implementation is still uncertain.

Public initiative with non-profit funding

88. **United Kingdom**

The Medical Research Council and the Wellcome Trust (a non-profit charity) propose to establish a voluntary database to be known as BIOBANK UK (previously called Population Biomedical Collection). BIOBANK UK will include the genetic details of 500,000 individuals, healthy volunteers between 45 and 65 years of age (i.e. who are likely to experience morbidity within one or two decades). At baseline, DNA samples, basic measurements, such as height, weight, and blood pressure will be taken, while details of medical history and lifestyle will be gathered from questionnaires. Patients will be followed up regularly throughout the study and the database will be updated with details of morbidity and cause of death in cohort members who die. Linkage between morbidity data, genotype, social status and lifestyles will identify gene-environment interactions in the causation of disease. Separate research groups would carry out genetic analyses on the volunteers, although the results would be held centrally to increase the value of the resource.

89. Approval for this database came in March 2001 from the House of Lords Select Committee on Science and Technology. A subcommittee of the select committee, chaired by Lord Oxburgh, set up in July 2001, investigated the present and future uses of human genetic databases. It took evidence from more than 55 medical institutions, drug companies, charities, and individuals. The report expressed strong support for the initiative from the Medical Research Council, with the



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Wellcome Trust and the Department of Health, to establish a large national database to study the interactions of genetic and lifestyle factors in the occurrence of disease. The committee also called for the setting up of an independent body, the Medical Data Panel, to safeguard the interests of individuals whose personal data are collected and held in genetic databases. The report stated: "The Data Protection Act 1998 offers significant protection to individuals over the use of their personal data. It is, however, the nature of research that there are always surprises around the corner... There may be future imperatives to use non-anonymous data in ways that could not be foreseen when samples are collected. It may often be impracticable . . . to consult individuals about this. Among our various recommendations, we propose a new independent body, the Medical Data Panel, to safeguard their interests." The report further recommends that the government provides "sufficient earmarked resources to the MRC and the Department of Health to ensure that the support and infrastructure required for this important initiative are in place." Committee members said that it was urgent that the National Health System (NHS) should adopt uniform standards and protocols for medical records, so they could be used in research.

90. Decisions and guidelines for expected commercial investment are yet to be formulated, but there is already concern (*The Observer*, September 23, 2001) that irrespective of the MRC/Wellcome initiative DNA samples will be taken routinely from hospitalized Britons, and used in commercial databases. The Human Genetics Commission (HGC) is planning to issue guidelines, but in the interim the Bioindustry Association has warned that unless access to NHS data is allowed, Britain will become a "third world genetics country".



List Of References And Internet Sources

Annas GJ (2001) Reforming Informed consent to Genetic Research. *JAMA* 286, 2326-8.

Bear JC. (2001) What is a person's DNA worth? Fair compensation for DNA access. 10th International Congress of Human Genetics, Vienna, May 2001 (bearre@mun.ca)

Beskow LM, Burke W, Merz JF et al. (2001) Informed consent for population-based Research involving Genetics. *JAMA*, 286, 2315-21.

Issa AM (2002) Ethical perspectives on pharmacogenomic profiling in the drug development process. *Nature Reviews*, 1, 300-8.

Shifman S, Bronstein M, Sternfeld M et al (2002) A highly significant association between a COMT haplotype and Schizophrenia. *Am J Hum Genet*, 71 (epub Oct 25, 2002)

For Appendix:

Iceland:

Annas GJ. (2000) Rules for research on human genetic variation--lessons from Iceland. *N Engl J Med*. 342,1830-3.

Gulcher JR and Stefansson K (2000) The Icelandic Healthcare Database and informed consent. *N Engl J Med*. 342(24):1827-30.

McInnis MG (1999) The assent of a nation: genetics and Iceland. *Clin. Genet*. 55, 234-239.

USA : Framingham:

http://www.mannvernd.is/english/news/nyt_framingham.html

http://199.97.97.16/contWriter/yhdweek/2001/01/02/medic/6711-0167-pat_nytimes.html

Sweden: UmanGenomics:

<http://www.umangenomics.com/>

Estonia:

<http://www.mannvernd.is/english/news/ft.estonia.html>

Hollon T, http://www.the-scientist.com/yr2001/feb/hollon_p1_010219.html

Tonga:

Hollon T, http://www.the-scientist.com/yr2001/feb/hollon_p1_010219.html

Burton, B. <http://www.commondreams.org/headlines02/0218-02.htm>

UK Biobank



Population-Based Large-Scale Collections of DNA Samples and Databases of Genetic Information

http://www.mrc.ac.uk/index/public_interest/public-consultation/public-biobank_consult.htm

MRC summary to the House of Lords committee:

http://www.mrc.ac.uk/pdf-hol_genetic_databases.pdf –

Fourth report of the House of Lords Select Committee on Science and Technology:

<http://www.parliament.the-stationery-office.co.uk/pa/ld200001/ldselect/ldsctech/57/5701.htm>

Canada, Quebec: Galileo Genomics

<http://www.galileogenomics.com/en/About.html>

Additional Reading:

Cook-Deegan R, Chan C and Johnson A (2001). World Survey of Funding for Genomics Research. *J Biolaw & Bus.*, Global Genomics and Health Disparities, 22-36.

Deschenes M, Cardinal G and Knoppers BM (2001). Human Genetic Research, DNA Banking and Consent: A question of "Form"? *Clin. Genet*, 59, 221-239.

Hodge JG and Harris ME (2001). International Genetics Research and Issues of Group Privacy. *J Biolaw & Bus.*, Global Genomics and Health Disparities, 15-21.

Maurer SM, Hugenholtz PB and Onsrud HJ (2001). Europe's Database Experiment. *Science*, 294, 789.

Omenn GS (2001). Special Challenges in Applying Genomics to Population Health. *J Biolaw & Bus.*, Global Genomics and Health Disparities, 3-6.

Winickoff DE (2001). Biosample Genomics and Human Rights: Context and Content of Iceland's Biobanks Act. *J Biolaw & Bus.*, Global Genomics and Health Disparities, 54-61.