Personalized Medicine, Population Genetics and Privacy:
An Empirical Study of International Gene Banks

By

Chad D. Holland

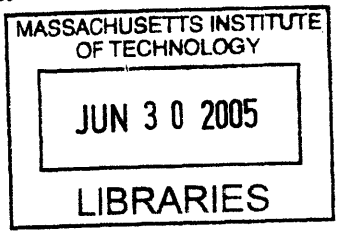
B.S. Chemical Engineering (1999), University of Wisconsin-Madison
M.B.A. (2004) Kellogg School of Management, Northwestern University

Submitted to the Sloan School of Management
and the Harvard-MIT Division of Health Sciences & Technology (HST)
in Partial Fulfillment of the Requirements for the Degrees of

Master of Science in Health Sciences & Technology
at the Harvard-MIT Division of Health Sciences & Technology

and

Master of Science in Management of Technology
at the Massachusetts Institute of Technology
June 2005



Signature of Author .....
Harvard-MIT Division of Health Sciences & Technology
16 May 2005

Certified by .....
Fiona E. Murray, Ph.D.
Assistant Professor, Thesis Supervisor

Certified by .....
Anthony J. Sinskey, Ph.D.
Professor, Thesis Supervisor

Accepted by .....
Martha L. Gray, Ph.D.
Co-Director, Harvard-MIT Division of Heatlh Sciences & Technology

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Introduction

The promise of personalized medicine lies in its potential to fundamentally change healthcare. In the past, pharmaceuticals were prescribed on a "one size fits all" basis—patients with certain disease phenotypes were given what were thought to be appropriate drugs. There is growing evidence however that the effectiveness of these drugs may differ by individual and by sub-group; presumably due to fundamental genetic differences in disease and metabolic pathways. Drugs like Herceptin, Gleevec and Iressa are part of an emerging trend in the biopharmaceutical arena of drugs that are accompanied by genetic diagnostic tests and prescribed only for patients with genotypes in which the agents are most effective.

Yet, such drugs represent only a first step in personalized medicine. The long-term vision of personalized medicine is to instead anticipate illness based on genetic risk, and then offer patient-specific treatment proactively to correct the problem before the patient falls ill. This transformation will likely be long in coming and will require those developing new drugs and treatments to explore a complicated mix of nature and nurture, of phenotype and genotype. The groundwork for our understanding of genotype has been laid with the sequencing of the human genome. However, untangling this relationship cannot be done through thought experiments or in isolated academic labs. Absent the study of real patients—their genetics as well as their health and family histories-- disease-related genes and mutations cannot be understood vis-à-vis healthy genes, in the context of the environment.

While there are significant technical challenges associated with this work, there are also a number of critical social and organizational issues that have not been addressed. In particular, in order to achieve this public good, firms must enroll the active participation of large numbers of people in population genetic studies. The fundamental challenge—and question of this thesis—is how to best design programs and institutions that ensure high levels of citizen-patient participation in personalized medicine studies and to prevent the organizational and social failure of these attempts. This thesis will examine six population genetic studies in five countries in an attempt to find preliminary answers to this question. The population genetic studies examined herein include: Quebec and Newfoundland in Canada (both of questionable success); Estonia (unsuccessful); Västerbotten, a county in the north of Sweden (unsuccessful); the UK (moving slowly) and the Icelandic case (successful).

Medical research studies involving human subjects have typically been organized as quasi-public efforts, with considerable control on the part of medical and scientific institutions: the scope of the study has been

limited, Institutional Review Boards have usually approved the research, and informed consent[1] has been received from the subjects. Furthermore, such research has typically occurred within the context of a "gift relationship"[2]. In such a relationship between physicians or scientists and patients, consenting patients give their time, tissue and data freely for the greater good of scientific research, for their own personal reasons, including perhaps a family history of a particular disease.

With the shift to large-scale population genetic studies, this gift exchange and the relatively unmediated scientist/physician relationship to participants has changed dramatically. It has shifted into a commercial context and, while money may not have changed hands, has shifted from gift exchange to more traditional exchange. Patients, physicians and various opposition groups have had a number of concerns about these large-scale, economically-oriented studies. One concern involves the potentially broad (and currently unknown) uses of the resulting database of information. Closely related is how confidentiality of such sensitive information is ensured, especially when DNA itself is a unique identifier. Sometimes, phenotypic data could be enough to betray an individual's identity. Other objections relate to the nature of the public discussion and debate surrounding the initiation of such studies—how the governments and/or companies consult the community, whether the approach was top-down or communicative, the substance of the debates, etc. Still other objections have to do with the nature of consent. As we shall see, Iceland passed a national law requiring the health and genealogical records of its entire population to be included in the study unless participants expressly opted out. (However, blood samples for DNA extraction were provided on an informed consent basis). Such an opt-out scheme provoked widespread criticism and prompted subsequent population genetic efforts to insist on opt-in consent.

A final controversy deals with the commercial nature of personalized medicine. Healthcare is a multi-trillion dollar industry. Because of the profound financial impact that personalized medicine promises to have on healthcare, population genetic studies are—always implicitly, though often explicitly—commercial in nature. For-profit companies either have built the databases associated with these studies themselves or could potentially license the results.

This thesis attempts to provide an understanding of the factors that have shaped the outcomes of several of the most critical population studies. It does so by placing these studies in the context of their transformation of the physician/scientist-patient interaction from a gift relationship to commercial exchange.

The findings have important implications for those in the pharma industry building strategies for personalized medicine. In particular they suggest that one key element of the strategy should include building the appropriate structures for relationships with population groups of interest. The findings presented here suggest that several elements should be in place: adequate measures to ensure informed consent as well as security and confidentiality of data; clear rules regarding IP; and a fair and open dialog (often best conducted by a democratic governmental process) to address issues of genetics and ethics in accordance with societal norms.

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[1] "The individual informed consent of a human research subject is generally required by law in the United States and in most other countries and by relevant international guidelines, such as the Helsinki Declaration of the World Medical Association...Exceptions involve research with no significant risk; research involving children and the mentally incompetent (whose parents or guardians must give consent); and, in a very few cases, research that by its nature cannot be conducted with informed consent, such as research on patients brought unconscious to hospital emergency departments after heart attacks. The patient (or guardian) need not only consent, but must do so after being informed of the nature of the research and of the specific benefits and risks it might hold for him. The requirement for informed consent grew from both respect for the individual's autonomy and the belief that an individual's informed consent would be one check on overly dangerous research". Greely, H. Informed Consent and Other Ethical Issues in Human Population Genetics. *Annu. Rev. Genet.*2001. 35:788

[2] Titmuss, R. *The Gift Relationship: From Human Blood to Social Policy*, Expanded and Update Editon. W. W. Norton & Company, Inc, New York: 1997.

Literature Review

Gift Exchange

Titmuss[3] in his classic comparative study of the blood bank industry argues that voluntary giving—the "gift relationship"--is central to the practice of medicine, and that one of its results is a more efficient system for blood banking than occurs in countries where the same activity is structured around the profit motive. "One of the principles of the [British] National Blood Transfusion Service and the National Health Service is to provide services on the basis of common human needs; there must be no allocation of resources which could create a sense of separateness between people...This case study of blood donor systems demonstrates the extent to which the policy values of the Service are held in common by the individual voluntary donor in Britain."

Titmuss describes many aspects of gift exchange, including:[4]

- The gift...takes place in impersonal situations, sometimes with physically hurtful consequences to the donor.
- The recipient is in almost all cases not personally known to the donor; there can, therefore, be no personal expressions of gratitude or of other sentiments.
- There are no personal, predictable penalties for not giving; no socially enforced sanctions of remorse, shame or guilt.
- For the giver, there is no certainty of a corresponding gift in return, present or future.
- Whether the gift itself is beneficial or harmful to an unknown recipient will depend to some extent on the truthfulness and honesty of the giver...
- Both givers and recipients might, if they were known to each other, refuse to participate in the process on religious, ethnic, political or other grounds.

While blood donors studied by Titmuss certainly possessed an underlying altruism, there was a mix of other sentiments as well. Some gave because they were grateful for good health; many others participated to reciprocate: because they or their loved ones received donations had received donations themselves—or thought they might in the future; yet others came out of a sense of duty; and a tiny number donated because they felt it gave them some benefit ("'From being a boy I had suffered from constant nose-bleeding and since I became a donor I have not had a single nose bleed'".) Gift exchange is therefore not necessarily characterized by pure altruism, but by giving freely so that a person or group of persons not known to the donor might benefit.

There are clear biomedical examples where the ethics of the gift relationship were not clear—or were clearly violated. Henrietta Lacks (after whom the HeLa cervical cancer cell line is named) and her family certainly felt so after doctors persuaded her to give tissue. Sonny Lacks, her son, complained that "[t]he

doctors tested us to see what was in my mother's system, was it hereditary...But that's all they said. They never got in contact with us again."[5] John Moore was similarly displeased when he found out that his spleen tissue had been cultured, patented, and was earning a significant licensing fee for the University of California.[6]

Most medical research, though, has been enabled by "the subject[s'] freely given informed consent"[7] to participate in studies. Human subjects engage in gift exchange with the physicians/scientists conducting the research, as well as the broader scientific community. While patients may in certain cases (e.g. early access to new drugs) directly benefit from participating in studies, the results oftentimes benefit others—and may involve significant risk to the subject. It has therefore been recognized that "[t]he voluntary consent of the human subject is absolutely essential."[8]

Informed Consent and Human Experimentation

> "Informed consent" is the voluntary agreement of an individual, or his or her authorized representative, who has the legal capacity to give consent, and who exercises free power of choice, without undue inducement or any other form of constraint or coercion to participate in research. The individual must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.[9]

Informed Consent—requiring the two elements of genuine understanding (informed) and willingness to participate (consent)--is a relatively modern invention. Hippocrates preached "benevolent paternalism: 'speak to the patient carefully and adroitly, concealing most things.'"[10] This view persisted. In Percival's "Medical Ethics" published in 1803, he states: "'To a patient who makes inquiries which, if faithfully answered, might prove him fatal, it would be a gross and unfeeling wrong to reveal the truth. His right to it is suspended, and even annihilated...'"[11] Percival's view was officially adopted by the American Medical Association in 1847.[12] Despite some court cases in the early and mid 20th century[13], informed consent and medical ethics only came to the forefront after the atrocities of Nazi medical experimentation were revealed in the post-World War II Nuremberg Trials.[14] "The Nuremberg Code was reflected in the Declaration of Human Rights and accepted in principle by each of the 51 original signatory nations of the Charter of the United Nations. At that time, most countries, including the United States, had no mechanism for implementing the provisions of the Code."[15] Further additions to the growing consensus on human research ethics were codified in the World Medical Association's Declaration of Helsinki in 1964.[16]

The US Belmont Report, issued in 1979, established three ethical principles of human experimentation:[17]

1. The principle of Respect for Persons acknowledges the dignity and autonomy of individuals, and requires that people with diminished autonomy be provided special protection. This principle requires that subjects give informed consent to participation in research. Because of their potential vulnerability, certain subject populations are provided with additional protections. These include live human fetuses, children, prisoners, the mentally disabled, and people with severe illnesses.

2. The principle of Beneficence requires us to protect individuals by maximizing anticipated benefits and minimizing possible harms. Therefore, it is necessary to examine carefully the design of the study and its risks and benefits including, in some cases, identifying alternative ways of obtaining the benefits sought from the research. Research risks must always be justified by the expected benefits of research.

3. The principle of Justice requires that we treat subjects fairly. For example, subjects should be carefully and equitably chosen to insure that certain individuals or classes of individuals -- such as prisoners, elderly people, or financially impoverished people -- are not systematically selected or excluded, unless there are scientifically or ethically valid reasons for doing so. Also, unless there is careful justification for an exception, research should not involve persons from groups that are unlikely to benefit from subsequent applications of the research.

Privacy

Privacy issues are central to population genetic efforts:

> The academic community relies on the availability of public databases for the distribution of the DNA sequences and their variations. However, like other types of medical information, human genomic data are private, intimate and sensitive. Genomic data have raised special concerns about discrimination, stigmatization, or loss of insurance or employment for individuals and their relatives...Public dissemination of these data poses nonintuitive privacy challenges.[18]

While computerized coding and encryption seem to offer part of the answer, many questions remain.[19]

Group Consent

Greely argues that, in addition to the ethical issues and challenges of individual informed consent, "[w]hat makes genetic research on populations different, and novel, is that the populations being studied are also, in effect, 'subjects' of the research. Those populations are collectively subject to possible benefits and harms from the research. These collective risks are beginning to be discussed by researchers and ethicists, but have yet to be well addressed by regulators."[20] While there are clear advocates and opponents of requiring group consent, the more pragmatic solution, especially after the controversy surrounding deCODE in Iceland, seems to be engaging in "group consultation"[21] through discourse with the community. These "discourse ethics" have been analyzed.[22,23]

Commercial Involvement

Commercialism poses a new challenge in the context of genomic research because it shifts the relationship between the donor and physician/scientist:

> Biomedical research has become more commercial in the past two decades; even academic researchers often have connections with for-profit companies. For some research subjects, the increased commercialization strains the altruistic basis for their participation. When the researchers hope to make millions of dollars from stock options from the application of their findings, the subjects may find it hard to accept satisfaction at helping humanity as their only reward. This conflict is even more pronounced with associational research. When genetics research is based on disease families, research subjects have a strong motivation to participate to help themselves and their kin. Associational genetic research, because of the weakness of the connections it seeks, has no such direct link to the health of a research subject or his family. At the same time, the high cost of genotype/phenotype resources makes it very likely that commercial firms are performing the research.[24]

This shift from altruistic, small-scale interactions between individual and scientists/physician to the participation in commercial studies with weak ties to an individual's own medical needs, raises a series of questions regarding the way in which participation can be secured and should be managed in this environment. These questions are of increased salience for many firms in the biopharmaceutical industry – not only those attempting to build commercial profits from population genetics, but also those who are attempting to incorporate personalized medicine and thus population-based genetics research into their strategic plans. Therefore, in this thesis we address the following questions:

- What were the strategies of successful and unsuccessful studies?
- How did these studies manage issues of consent, oversight, enrollment and intellectual property?
- What were the key sources of debate and tension, and what were best practices to resolve them?
- What was the outcome of each study?

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[3] Titmuss, R. *The Gift Relationship: From Human Blood to Social Policy*, Expanded and Update Editon. W. W. Norton & Company, Inc, New York: 1997.
[4] Taken verbatim from Titmus, R., ibid. Pages 127-128.
[5] Skloot, R. Henrietta's Dance. *Johns Hopkins Magazine*, April 2000. Available online at http://www.jhu.edu/~jhumag/0400web/01.html (accessed 14 May 2005).
[6] See, for example http://www.rasmusen.org/w/04.06.14d.htm (accessed 14 May 2005).
[7] World Medical Association, Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Originally adopted in June 1964 and amended a number of times, most recently in 2000. Available online at http://ohsr.od.nih.gov/guidelines/helsinki.html (accessed 13 May 2005).
[8] Nuremberg Code, Directives for Human Experimentation. Reprinted online at http://ohsr.od.nih.gov/guidelines/nuremberg.html (accessed 13 May 2005) from *Trials of War Criminals before the*

Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181-182.. Washington, D.C.: U.S. Government Printing Office, 1949.

[9] Levine, R.J. "Ethics and Regulations of Clinical Research." New Haven: Yale University Press, 1988. Quoted at http://www.cc.nih.gov/ccc/protomechanics/chap_3.html (accessed 13 May 2005)

[10] See University of Washington MHE 523 Session #7 course presentation, available online at http://courses.washington.edu/mhe523/Session7.ppt#3 (accessed 13 May 2005)

[11] See http://courses.washington.edu/mhe523/Session7.ppt#5 (accessed 13 May 2005)

[12] http://courses.washington.edu/mhe523/Session7.ppt#8 (accessed 13 May 2005)

[13] http://courses.washington.edu/mhe523/Session7.ppt#9 (accessed 13 May 2005)

[14] Resulting in the Nuremberg Code, ibid. Text below:

Directives for Human Experimentation

NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

[15] See Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health, available online at http://ohsr.od.nih.gov/guidelines/GrayBooklet82404.pdf (accessed 14 May 2005)

[16] Declaration of Helsinki, ibid.

[17] Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health, ibid.

[18] Lin, Z. Genomic Research and Human Subject Privacy. *Science*, vol 305, 9 July 2004.
[19] Callan, B and Gillespie, I. Biobanks: From health protection to data protection. *OECD Observer*; Dec 2003; 240/241.
[20] Greely, H. Informed Consent and Other Ethical Issues in Human Population Genetics. *Annu. Rev. Genet.* 2001. 35:785-800.
[21] Greely, H. Informed Consent, ibid.
[22] Racine, E. Discourse ethics as an ethics of responsibility: comparison and evaluation of citizen involvement in population genomics." *Journal of Law, Medicine & Ethics*. Vol 31, Iss 3, 22 Sept 2003.
[23] Petersen, A. Securing our genetic health: engendering trust in UK BIobank. *Sociology of Health & Illness*, vol 27 no. 2, 2005.
[24] Greely, H. Informed Consent, ibid.

Methodology

The questions outlined above are generated from both an examination of the prior literature in the field of gift exchange and an understanding of the key contractual elements (and controversies) that dominate the management of human subject research in medical settings. However the current literature, being largely based on debates over medical practice and research ethics, have little advice to provide a researcher in building hypotheses regarding whether and how human subjects will respond to changes in the gift exchange relationship. Therefore, in studying the elements of this transformation we turn instead to inductive theory building and an examination of prior examples. The use of case studies can be an extremely valuable methodology for novel areas of research with little prior research and few realistic hypotheses. However the success of this approach turns on the careful choice of cases and comparative case experimental design. In order to address the questions posed in this thesis, I have chosen six case studies each of which represents an example of a previously academic/gift-oriented population study being transformed into a large-scale commercial population genetics project. These six cases represent the largest and best-known projects of their type but given their geographic diversity and the diversity of participants there is no reason to believe that they are associated with any systematic biases. Furthermore, these cases vary in the success of their outcomes, in terms of actually gaining access and participation – thus we avoid sampling on the dependent variable. Therefore, the six matched cases, constitute a "natural experiment" of sorts and can be used as the basis for an inductive study and grounded in theory building. The six cases studied (Quebec and Newfoundland in Canada, Estonia, the UK, Sweden and Iceland) are all structured in such a way as to examine the following elements:

1. What were the conditions in the regions pre-biobank? In some cases, there had been extensive prior genetic study in the country; in other cases, minimal. Most of the cases involved early public efforts and gift exchange between study participants and the scientific/medical community.
2. Something happened to disrupt the status quo. While this change was enabled by broad scientific developments, specific events and/or people in the country catalyzed the change. The change often involved movement to a commercial structure or involvement from commercial entities.
3. What were the results of the change? How successful was the resulting biobank effort and what factors contributed to the ultimate success or failure?

The detailed insights gained from these cases will allow us to examine the shift from gift to commercial exchange and develop insights into key issues for debate and key parameters that played a role in a program's ultimate success or failure.

This study reports the findings of extensive empirical research, drawing from the scientific and other academic (law, sociology) literature, the lay press and one personal interview.

UK Biobank

History of the UK and its Population

The first settlers in the UK left no evidence of their existence there, but were suspected to have established themselves after the first ice age. They were hunter gatherers and survived for 100 centuries before the first farmers came onto the scene about 6000 years ago.[25] Early tribes included the Caledonii in Scotland, Iceni from East Anglia and the Brigantes in north England.[26] Today, we call these tribes Celts, a term that came into vogue around 1700 when it was discovered "that the non-English island tongues relate to that of the ancient continental Gauls, who really were called Celts. This ancient continental ethnic label was applied to the wider family of languages. But 'Celtic' was soon extended to describe insular monuments, art, culture and peoples, ancient and modern: island 'Celtic' identity was born, like Britishness, in the 18th century."[27]

The inhabitants were brought under Roman control between 43 AD and 82 AD under Emperor Claudius. While Roman soldiers constituted only a small portion of the population, the Romans had a strong influence on the culture and politics of the British Isles until their withdrawal in 410 AD. The population was left to fend for themselves against Jutes, Angles and Saxons from today's Denmark and Germany. These Anglo Saxons invaded in the south and east coasts, subjugating parts of the population and displacing others.

Vikings from Scandinavia began attacking and invading in 793. "The best guide to Scandinavian settlement are the place names they have left behind such as places ending with '-by' and '-thorpe'."[28] The Normans, led by William Duke of Normandy (William the Conqueror) attacked at the Battle of Hastings in 1066 and began slowly taking control of the land through the early medieval period.

> In 1348, the Black Death (or Bubonic Plague) arrived in Britain through the ports of southern England. The disease was transmitted to humans by fleas carried in the fur of rats.
>
> The symptoms were high fever and inflammation of the groin and armpits. Few recovered from the disease and most died within three days of showing the first symptoms.
>
> From southern ports, the plague spread across the country, reaching London by September 1348 and the Scottish Highlands by the autumn of 1349. London lost nearly half its population due to the disease and, in some Cambridgeshire villages, the death toll may have been nearer seventy-five per cent. Some hamlets lost so many of their adult population that they never recovered and became deserted.

> Only in the colder climate of Scotland did the plague fail to make such devastating impact (although between a sixth and a fifth of the Scottish population may have been killed). Over the next three centuries, the plague returned numerous times in local and national epidemics. In 1665, London suffered its last major outbreak with an estimated 70,000 of the capital's population of half a million dying).[29]

Famine, war and sickness restricted the population growth during the period after the major spells of the Black Death and before the Renaissance. After the Renaissance, the country was immersed in Civil War from 1642 until 1649. England and Scotland lost four and six percent of their populations, respectively, and Ireland may have lost as much as 20%.

After this, the country's population grew rapidly during the subsequent two centuries during urbanization and revolutions in industry and agriculture. However, the British population lost significant number to emigration to the New World and the Irish potato famine in the 19th century (though mainland Britain did gain Irish and various Eastern Europeans), then again to two world wars in the first part of the 20th century. Only after the Second World War did significant numbers of immigrants arrive from Africa, Asia and the Caribbean.

In short, these various waves of conquest, immigration, death and emigration resulted in today's heterogeneous population of about 60 million.[30]

Previous Genetic Work with Population

The UK has played a central role in research in biotechnology and genetics. The structure of DNA was first elucidated there in 1953, and Prime Minister Tony Blair is proud to report that, since that time, "[Britain's] record continues to be outstanding; with just one per cent of the world's population, we receive nine per cent of scientific citations. Nowhere has this record been more notable in recent decades than in bio-science and bio-technology."[31]

The UK has thus been active in gene hunting and other research involving population studies. Topics of study included: obesity,[32] multiple sclerosis,[33] inflammatory bowel disease,[34] cancer,[35] Huntington's Disease, reading disability, endometriosis,[36] rheumatoid arthritis,[37] cystic fibrosis,[38] and others. Industry research has also been active. For example, UK company Gemini Genomics was actively engaged in genetic studies of a number of diseases in twins in the UK and abroad.[39] The company was subsequently bought by U.S.-based Sequenom.[40]

The UK's National Health Service (NHS) has played a major role in population genetics research:

> Historically, the structure of the NHS has facilitated academic research in clinical genetics, generating family material for gene mapping, pedigree analysis, and related research. This role was weakened in the early 1990s by the internal market reforms of the NHS, which led to organizational fragmentation and disparate priorities by creating autonomous geographic zones and independent health authorities, with minimal imposition of demands for uniform clinical standards. The recent Government White Paper's objective of abolishing the internal market is an encouraging sign that the continuation of academic genetics research is feasible. But much more is possible.
>
> The NHS is a high-quality health care system that provides a comprehensive service to everyone in the United Kingdom (59 million people). It also provides a research resource, assembled over 50 years, comprising detailed patient records and archived tissue samples for constructing disease libraries. The NHS is probably the largest single source of medical information and well-characterized biological samples in Europe and encompasses substantial subpopulations of important ethnic groups. In addition, it represents a significant research resource in terms of clinical expertise and infrastructure. NHS records provide a large longitudinal population database that is of great potential value for genetic epidemiology, for the clinical analysis of risk traits, and for correlating genotype-to-phenotype patterns of disease progression and treatment outcomes. The potential biases created by the selective study of small family pedigrees or isolated populations justify an ambitious strategy to define the risks associated with particular genomic profiles in larger outbred populations.[41]

The UK Biobank: What It Is and How It Will Work

The UK Biobank is a Company Limited by Guarantee and a Registered Charity. The project "...will become the world's biggest resource for studying the role of nature and nurture in health and disease" by tracking up to 500,000 participants between 45 and 69 years of age.[42] The project is set up as a prospective cohort study (compares versus a case-control design, where those with a disease—the "cases"—are compared to those "controls" without) and will track the health of participants for 30 or more years. "The UK Biobank resource will allow researchers to examine [the interplay among genes, environment and lifestyle] and determine the impact of genetic and environmental factors on disease risk and progression."[43]

It is not entirely clear how volunteers will be obtained. One source suggests that volunteers will be recruited through their primary care general practitioners (GP's) with the help of trained nurses.[44] Another suggests that "participants identified from health registers will be invited to take part in the project."[45] It is not entirely clear, then, how patients will be selected and consequently, to what extent the composition of the sample of 500,000 will be representative of the broad UK population of 60 million.

Regardless of the method used to recruit, those patients who choose to participate will give their consent[46] (opt-in), then give blood and urine samples, take a basic physical exam (blood pressure, height and weight), and answer a health and lifestyle questionnaire. (Note that consent is expected to be blanket: that

is, patients are either "in" or "out" of the biobank and are expected to be allowed, for example, to elect to participate in certain studies but not in others. Patients will always have the opportunity to withdraw from the study. However, there may be three different ways in which a patient might withdraw[47].) After samples are take, they will be then be coded (anonymized) and stored. Researchers whose projects had been approved by Biobank (and its associated committees—process was still in flux) will then be able to access only the anonymous samples and data.[48] Patients may be contacted for follow-up by the Biobank, but never directly by a researcher. Data would also be gleaned from volunteers' medical records on an ongoing.

It was also stressed that the Biobank was considered a research initiative and not a healthcare program. As such, patients would receive no personal information or advice on their health or disease status from the program. Patients would also not be paid for their efforts and would forgo any intellectual property that might arise from the biobank.

Note that the logistical specifics of many of these steps were not yet defined.

Initiation of the UK Biobank

> The idea for Biobank began in 1998 when a UK government spending review gave the Medical Research Council (MRC) additional funds to set up "nationally available DNA collections…In May, 1999, a workshop on a UK population biomedical collection was held, after which [see Figure 1] an expert working panel was convened chaired by Prof Tom Meade of the London School of Hygiene and Tropic Medicine. This panel recommended in a report published in March, 2000, the setting up of two prospective population cohort studies: the first of 500 000 middle aged individuals; the second a 20 000-50 000 birth cohort. The former was felt to be of the higher priority and more likely to provide results quickly (ie, disease would develop faster in this age range), and the idea of the birth cohort was dropped. From this point on the prospective cohort study design was fixed. A protocol development committee, again chaired by Meade, was then set up to work out the details of the 500 000 middle aged cohort. This committee had several disagreements, for example on the importance of accurately establishing the baseline phenotype of the individuals–particularly important for endocrine, cardiovascular, and respiratory diseases. Some committee members believed that unless this phenotyping was sufficiently detailed, very little information that was pertinent to these diseases could be produced. Other members of the committee believed that the study design should attempt to enrich for ethnic minorities; some others have argued that a familial cohort should be recruited.
>
> However, the protocol that was sent for peer review to 12 mostly non-UK reviewers contained none of these substudies. Most reviewers apparently made positive comments on the study design (the comments are not available for public scrutiny; indeed most members of the protocol development committee did not see them). Some dissenting members of the committee produced a supplementary proposal that was a scientific justification for intensively phenotyping a cohort of 40000 participants. This proposal was also peer reviewed, and judged scientifically valid by the reviewers, but was not included in the draft protocol published in February, 2002, possibly

because of the amount of extra money involved (£8-10 million). The estimated initial cost of the project (£30-40 million) was already high, and any extra amount needed was not thought to be politically justifiable, and could have led to the whole plan being abandoned. In parallel with these scientific reviews, several ethics and public consultations were held, some of which are shown in [Figure 1].[49]

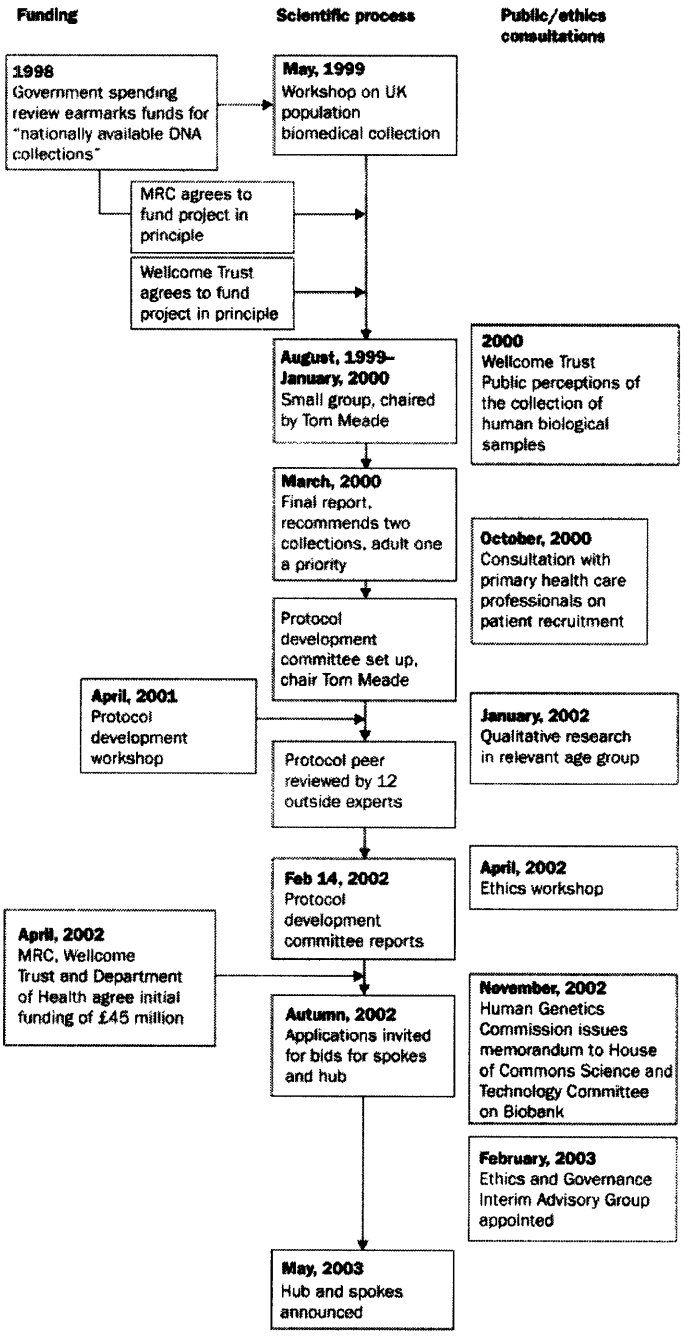

Figure 1: Timeline of development of UK Biobank through May 2003. Compiled from information on the Biobank website (www.biobank.ac.uk, accessed May 1, 2003). Source: Barbour, V. UK Biobank: a project in search of a protocol? Figure 2. *The Lancet* vol 361, p. 1736. 17 May 2003.

Biobank Structure and Funding

In April 2002, the initial budget was set at £45 million over seven years, with the MRC and Wellcome Trust each contributing £20 million and the Department of Health the remaining £5 million. These amounts accounted for only a tiny portion of the MRC budget and also a small part of the Wellcome's £110 million allocated for functional genomics.[50,51] In 2003, these numbers increased to £28 million each from the Wellcome Trust and MRC, £5 million from the Department of Health, plus an additional £500,000 from the Scottish Executive for a total development budget of about £61 million.[52] "After seven years the project is expected to be self-financing. It may also be eligible for some funding to cover costs incurred by the NHS through the Department of Health's Support for Science scheme."[53]

In July 2002, the Biobank moved ahead with preliminary meetings for institutions interested in hosting "regional collaborating centers" and the "coordinating center" (formerly called "spokes" and "hub", respectively).[54] The interested institutions underwent a bidding process[55], the winners of which were announced on 7 May 2003. The coordinating center was based in Manchester, with six regional collaborating centers helping direct the activities 23 universities.[56] The "Manchester headquarters of the study of genes, environment and health, will have overall responsibility for delivering the project including data management and quality assurance, computing and financial management. It will also be responsible for co-ordinating the activities of six scientific Collaborating Centres who will contribute to the design of the project and be responsible for participant recruitment and initial data and sample collection."[57]

An "Ethics and Governance Framework" laid out, among other things, the governance structure of the Biobank. Three internal bodies were involved in running the Biobank: an Ethics and Governance Council (EGC), the Science Committee, and the Board of Directors. It was also proposed to have an independent external committee on medical research ethics to help review proposals to use the Biobank's data and samples. However, the specifics of how exactly the review process and general project governance worked was a source of much confusion and concern.[58]

> The development of the Ethics and Governance Framework was undertaken by a specially commissioned interim advisory group that comprised lawyers, social scientists, clinicians, ethicists and lay representatives. Their work incorporated information from several consultative exercises with public and professional groups. When the draft framework was published, the funders of the UK Biobank...allowed a short period during which interested parties could comment on it.[59]

As noted above, the tissue samples and database will not belong to the donors; instead, the UK Biobank "will serve as the steward of the resource, maintaining and building it for the public good in accordance

with its purpose."[60] In practice, this probably means licensing the bank to public and private users for a fee that is higher for private companies and lower for academic research. Fees will accrue to the Biobank.

Criticism

The project has sought much public input and received much solicited[61,62] and unsolicited feedback. Some critics have been organized groups such as GeneWatch UK, which suggested that that the Biobank had "'unclear benefits to individuals and society.'"[63] Many other criticisms have been made, including:[64]

- Lack of clarity of the legality of police access to the database
- The involvement of the private sector, especially the chance of sensitive information being used against donors by insurance companies, employers, et al.
- Whether the Biobank is the best use of limited resources
- Validity of the scientific design (non-hypothesis based)
- How contracts were awarded

The House of Commons' Select Committee directly attacked the sincerity of the Biobank's many public consultations:

> It is our impression that the MRC's consultation for Biobank has been a bolt-on activity to secure widespread support for the project rather than a genuine attempt to build a consensus on the project's aims and methods. In a project of such sensitivity and importance consultation must be at the heart of the process not at the periphery.[65]

One sociologist commented:

> As in the US, the emergence of commissions as decision-makers and an emphasis on a 'principle'-based system of ethics has served to 'thin' public debate...Substantive ('thick') debates about the ultimate ends of human genetic research are obscured by a focus on formal rational (and universalist) arguments about the most efficacious means of achieving predetermined or assumed ends such as autonomy...The question of how to best ensure 'informed consent', for example, has been posited as a fundamental issue confronting UK Biobank, despite recognized difficulties of applying principles of consent, which were developed in the medical context, to population collections...[66]

Current State of the Project & Conclusion

Despite the announcement[67] in December 2004 of CEO John Newton's intention to resign in March 2005, the project appears on track. In March 2004, it was announced[68] that the Ethics and Governance Framework (EGF) was being revised based on feedback; however, no revised version appeared on the website as of May 2005. In November 2004, the independent Ethics and Governance Council, chaired by Alastair Campbell, was in place.[69] A Phase I pilot study (simply to investigate patient flow and consultation issues; no samples to be taken) was to begin in February 2005. "Later in the year [the

Biobank] will undertake more widespread recruitment into the larger Phase 2 Pilot study, before beginning work on the main project in 2006."[70]

The project is therefore in an early stage. Its ultimate success remains to be seen.

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[25] James, S. People of Britain. Available online at http://www.bbc.cok.uk/history/ancient/prehistory/peoples_print.html (accessed 2 May 2005)
[26] BBC History. Available in the form of an online animation: http://www.bbc.co.uk/history/society_culture/society/launch_ani_population.shtml# (accessed 2 May 2005)
[27] James, S. Ibid.
[28] BBC History, ibid.
[29] BBC History, ibid.
[30] Source of population: *CIA World Factbook*. Available online at http://www.odci.gov/cia/publications/factbook/geos/uk.html#People (accessed 04 May 2005)
[31] UK Department of Health. Our Inheritance, Our Future: Realising the Potential of Genetics in the NHS. June 2003. Available online at http://www.dh.gov.uk/assetRoot/04/01/92/39/04019239.pdf (accessed 4 May 2005).
[32] Cahllis, BG. The CART gene and human obesity: mutational analysis and population genetics. *Diabetes.* 2000 May 49(5)872-5.
[33] Heggarty, S. A genome wide scan for association with multiple sclerosis in a N. Irish case control population. *J Neuroimmunol.* 2003 Oct; 143(1-2):93-6.
[34] Mathew, CG. Genetics of Inflammatory Bowel Disease: Progress and Prospects. *Hum Mol Genet.* 2004 Apr 1; 13 Spec No 1:R161-8
[35] See, for example, http://www.imm.ox.ac.uk/pages/research/cancer_research/colorectal.htm (accessed 14 May 2005)
[36] See http://bioinformatics.well.ox.ac.uk/%7Elon/ (accessed 14 May 2005)
[37] http://www.arc.org.uk/newsviews/press/H0648.htm (accessed 14 May 2005)
[38] http://www.cardiff.ac.uk/medicine/medical_biochem/cystic_fibrosis/ (accessed 14 May 2005)
[39] S.G. Cowen Analyst report, Gemini Genomics, dated 21 Aug 2000.
[40] http://www.sequenom.com/ (accessed 14 May 2005)
[41] Fears, R and Poste, G. Building Population Genetics Resources Using the U.K. NHS. *Science*, Vol 284, Issue 5412, 267-268 , 9 April 1999
[42] The UK Biobank briefing note. A study of genes, environment and health. April 2004. Available online at http://www.ukbiobank.ac.uk/docs/long_briefing_paper.pdf (accessed 2 May 2005)
[43] The UK Biobank briefing note, ibid.
[44] Barbour, V. UK Biobank: a project in search of a protocol? *The Lancet* vol 361, p. 1736-1738.
[45] The UK Biobank briefing note, ibid.
[46] What does 'consent' mean? (verbatim from The UK Biobank Ethics and Governance Framework Version 1.0, 24 Sept 2003. Available online at http://www.ukbiobank.ac.uk/docs/egf-comment-version.doc accessed 2 May 2005.)

Consent

Consent will be sought "to participate in UK Biobank". Participation will be cast as an opportunity to contribute information that in the long term may help enhance other people's health. Because it will be impossible to anticipate all future research uses, strong governance and safeguards will be in place to protect participants' interests and the public interest.

Consent will be based on an explanation and the understanding of, amongst other things:

- the purpose of UK Biobank
- the fact that UK Biobank is not a healthcare programme but a research resource

- the kinds of information and samples that will be collected at enrolment, which may include data that some participants might consider especially sensitive
- the fact that there will be a link to the full medical record, past and ongoing
- the fact that UK Biobank will be the legal owner of the database and the sample collection, and that participants have no property rights in the samples
- the kinds of safeguards that will be maintained, including secure storage of data and samples in reversibly anonymised form (as explained in section I.C.2), and severe restrictions on access to data and samples that are not anonymised
- the policy for making decisions on research access
- the assurance that only research uses that have been approved by both UK Biobank and an NHS Multi-centre Research Ethics Committee (MREC) will be allowed, and that data and samples will be anonymised before being provided to research users
- the expectation that commercial entities will apply to use UK Biobank
- the possibility of being recontacted in future, by whom and for what purposes
- the need for UK Biobank to retain as many participants for as long as possible in order to maximise its value as a research resource
- the intention to continue to hold and allow research access to data after participants lose mental capacity or die, as such data are crucial for research on severe illnesses
- the right to withdraw at any time without having to give a reason and without penalty, and the meaning of withdrawal
- UK Biobank's commitment to maintaining active engagement with participants and society in general.

The points listed above are some elements of what it means "to participate in UK Biobank"; each is discussed in more detail later in the Framework. These elements and other customary undertakings will be addressed in participant information and the consent process.

UK Biobank will endeavour to make sure that participants understand what they are consenting to. Ways of doing this may be tested in an independent evaluation of the consent process used during the pilot phase.

The consent to participate in UK Biobank will apply throughout the lifetime of UK Biobank unless the participant withdraws. Further consent will be sought for any proposed activities that do not fall within the existing consent.

[47] (The note that follows is taken verbatim from UK Biobank Ethics and Governance Framework Background Document, 10 Oct 2003. Available online at http://www.ukbiobank.ac.ak/docs/egf-background.doc accessed 2 May 2005):

Right to withdraw

From the beginning, withdrawal was seen by the IAG as a right to be guaranteed by UK Biobank. What did not become clear for a while was that this could take several forms. Then the IAG realised that a few participants might want data about themselves or samples to be destroyed, that a few might want no further data to be collected but

wouldn't mind continuing use of whatever was already in the resource, and that some might simply want not to be contacted any more. Consequently the EGF outlines the three versions of withdrawal, from the most to the least serious:
(a) complete withdrawal; (b) discontinued participation; (c) no further contact requested.

The principle of voluntariness requires that participants be allowed to withdraw with little effort, at any time, and without having to give a reason.

[48] Setting Standards. The UK Biobank Ethics and Governance Framework. 24 September 2003. Available online at http://www.ukbiobank.ac.ak/docs/egf-summary.doc (accessed 2 May 2005)
[49] Barbour, V. Ibid.
[50] See http://www.ukbiobank.ac.uk/about/2002.php (accessed 2 May 2005)
[51] Barbour, V. Ibid
[52] See Ethics and Governance Framework for UK Biobank Published for Comment. Wellcome Trust press release, 22 Sept 2003. Available online at http://www.wellcome.ac.uk/doc_WTD002848.html (accessed 2 May 2005)
[53] The UK Biobank briefing note, ibid.
[54] See http://www.wellcome.ac.uk/doc_WTD002848.html (accessed 2 May 2005)
[55] How contracts were awarded (quoted verbatim from Barbour, V, 2003. Ibid.):
The bidding process that has just finished for the hub and spokes has, by all accounts, been inordinately time-consuming for the many scientists who took part. Two individuals involved said it was more akin to bidding to build a bridge or a motorway rather than to do a scientific project. The forms that applicants were required to fill in were not primarily concerned with science. Applicants were asked to show that they were able to provide the necessary organisation, experience, and infrastructure for the project, and that their institutions were financially sound. Each application required a prequalification questionnaire that ran to several hundred pages, and then a formal application of a similar size. The leader of one bid estimated that it took up most of his time for several months. The process was surrounded by secrecy as rival institutions were warned that they should not discuss details for the bids, and had to sign confidentiality agreements. A spokesman for the project told *The Lancet* that these conditions were imposed following legal advice that, because of the large sums of money involved, Biobank should adhere to European Union procurement rules on tendering to prevent the formation of cartels. Because most scientists are used to working collaboratively, many felt very uneasy about this secrecy.

What has not yet been made clear is what role those not selected to be involved as hub or spoke institutions will have in shaping Biobank. By not including them the project might lose much needed goodwill, and would miss out on the contribution of many experienced scientists. It seems that the project's funders are beginning to address this problem. A recent meeting of those selected to be spokes was told that there was every intention of being as inclusive as possible and that every effort should be made to involve "the best minds in science".

[56] The following academic and research institutions make up the consortia for each of the Collaborating Centres (source: Wellcome Trust press release 7 May 2005, UK Biobank Enters New Phase. Available online at http://www.wellcome.ac.uk/doc_WTD002901.html accessed 2 May 2005):

1. North West Wessex Consortium
Manchester - Keele Universities' Medical School
University of Southampton Medical School Southampton (MRC Environmental Epidemiology Unit)

2. Scottish Consortium
University of Glasgow
University of Edinburgh
University of Aberdeen
University of Dundee
(all Academic Departments of Primary Care)

3. Welsh Consortium
Centre for Health Sciences Research
University of Wales College of Medicine, Cardiff

Swansea Clinical School, University of Wales, Swansea
University of Wales, Bangor

4. London Consortium
Imperial College London
University College London
Kings College London
Queen Mary University of London

5. Fosse Way Consortium
University of Leicester
University of Birmingham
University of Bristol
Warwick Medical School
University of Nottingham
Peninsula Medical School
University of Sheffield

6. Central England Consortium
University of Oxford

[57] UK Biobank Enters New Phase, ibid.
[58] UK BIOBANK Ethics and Governance Framework: Summary of comments of Version 1.0. May 2004. Available online at http://www.wellcome.ac.uk/assets/WTD003285.pdf (accessed 2 May 2005).
[59] Tutton, R. et al. Governing UK Biobank: the importance of ensuring public trust. *TRENDS in Biotechnology*, vol 22 no 6, June 2004.
[60] UK BIOBANK Ethics and Governance Framework: Summary of comments of Version 1.0. Ibid.
[61] UK BIOBANK Ethics and Governance Framework: Summary of comments of Version 1.0. Ibid.
[62] See various commissioned studies and reports through People Science & Policy, such as The UK Biobank—A Question of Trust (http://www.peoplescienceandpolicy.com/biobank.html); The UK Biobank—A consultation with nurses in general practice and research (http://www.peoplescienceandpolicy.com/biobank-nurses.html) and The UK Biobank—Consultation on Ethical and Governance Framework (http://www.peoplescienceandpolicy.com/biobank-consultation_on_egf.html). All three sites accessed 2 May 2005.
[63] GeneWatch UK challenges the MRC, Wellcome Trust and Department of Health to allow an independent scientific peer review of Biobank UK. GeneWatch UK press release dated 22 April 2002.
[64] Petersen, A. Securing our genetic health: engendering trust in UK Biobank. *Sociology of Health & Illness*. Vol 27, no 2, pp. 271-292. 2005.
[65] House of Commons Select Committee on Science and Technology. *Third Report*, March 2003. Quoted in Petersen, A. (ibid).
[66] Petersen, A. Ibid.
[67] See http://www.ukbiobank.ac.uk/docs/UKBIOBANKSTATEMENT_000.pdf (accessed 4 May 2005)
[68] See http://www.ukbiobank.ac.uk/news/archive.php (accessed 5 May 2005)
[69] http://www.wellcome.ac.uk/doc_WTX022802.html (accessed 5 May 2005)
[70] http://www.ukbiobank.ac.uk/about/P1Pinfo.php (accessed 5 May 2005)

Canada: Quebec and Newfoundland

About Canada and its populations

Quebec

Beginning in the 1600's, immigrants from various parts of France colonized North America, creating two separate French populations in the New World. One group, called the Acadians, settled on the Bay of Fundy until the British scattered the group in the 1750's. "The Acadians retained a lively culture and identity, and their forced diaspora had genetic consequences in the twentieth century, notably, clustering of Mendelian disorders among the Acadians, among those who settled anew in Louisiana (the Cajuns), and those who resettled in Canada, some 4000 of them in Quebec."[71]

The other group of French settlers founded what was referred to as *Nouvelle France*, founding Quebec City in 1608 and growing the population of the region through immigration until 1660. After that point, most population growth was from reproduction.[72] The area became British territory in 1759, during the Seven Years War. Between 1608 and 1759, approximately 8500 individuals (1600 women, though 90% of settlers produced offspring)[73] arrived and stayed permanently in the area—the founding population. *Nouvelle France* was referred to as Lower Canada after 1841 and eventually became Quebec. Because of language and religious differences, the founding group remained relatively isolated. Today, about six million of Quebec's 7.3 million people are direct descendents from the original population of 8500. (Note, however, that some sources[74,75] suggest that the founding population was only 2,500-2,600 individuals. It is unclear where this disparity comes from.)

This population therefore has was have been arguably called "'optimum characteristics for gene discovery in each of the key criteria.' These include a large number of generations since founding (14 generations), a small number of founders...a high rate of population expansion (74 percent per generation), a large population today...and minimal intermarriage."[76]

Quebec has a high rate of Mendelian (monogenic) disorders for a number of conditions, including cystic fibrosis, familial hypercholesterolemia, pseudo-vitamin D deficiency and cystic fibrosis. See Canada Canada Appendix A for a more complete list of these Mendelian phenotypes.

There is a history of earlier genetic research in Quebec, reported in the literature as early as the early/mid 1970's. One article in May 1973 analyzed "[t]he frequency of genetic disease and congenital

malformation among patients in a pediatric hospital"[77], while another talks about the endowment of a new genetic center at Shriners Hospital.[78] By the 1990's, Quebec seemed to be deeply engaged in a broad range of genetic research. One major study seems to have been The Quebec Family study, which looked at variety of cardiovascular risk factors over a number of families from Quebec.[79] In addition to individual, disease and family studies, Quebec played a role in Canada-wide and international efforts under the auspices of national- and province-level funding organizations. These efforts are discussed in more detail below.

Newfoundland

Archeological evidence points to three early groups in Newfoundland, an island group in the easternmost part of Canada: Beothuk Native Americans, Maratime Archaic Indians and Paleo Eskimos. Celts and Norse also explored the area; however, none of these five groups left lasting settlements.[80]

> John Cabot first reached Newfoundland in 1497 and seasonal colonies were first established around 1610. The peak immigration to Newfoundland occurred in the mid-1700s, and included mainly Protestant settlers from the south-west of England and Roman Catholic settlers from the south of Ireland. Starting from about 20 000 settlers in 1760, the population grew by natural expansion to ~200 000 in 1890. The present population of the province of Newfoundland and Labrador is 512 930, with 98% of English or Irish descent. Sixty percent of the current population of Newfoundland resides in communities with 2500 inhabitants or less [See Figure 2]. This fact is important for genetic studies, as the average kinship between subpopulations generally decreases with the distance between them; geographic distance is a major determinant of genetic isolation. This rate of expansion is similar to that of other recently founded isolates that have been the focus of genetic mapping studies.[81]

Newfoundland has been very isolated: in addition to its geographic isolation, it became part of Canada very late—in 1949.[82] This homogenous population (some have gotten in trouble for calling it "inbred")[83] has high rates of a number of genetic-related diseases. The population-wide prevalence of psoriasis has been estimated as high as 10%.[84] Other significant diseases in the population include rheumatoid arthritis and diabetes.[85]

The province is rich in natural resources, such as oil, gas, minerals and timber. The economy had also been based heavily on cod fishing, an industry which imploded in 1992, causing unemployment to soar. "The disparity in natural and real wealth has turned the province, as *Toronto Mail and Globe* columnist Jeffrey Simpson derisively wrote, into 'a culture of grievance.' Many Newfoundlanders say [the national government in] Ottawa has plundered their natural resources through a flawed political process, pocketed too much of the profit, and left them to grovel for their fair share."[86]

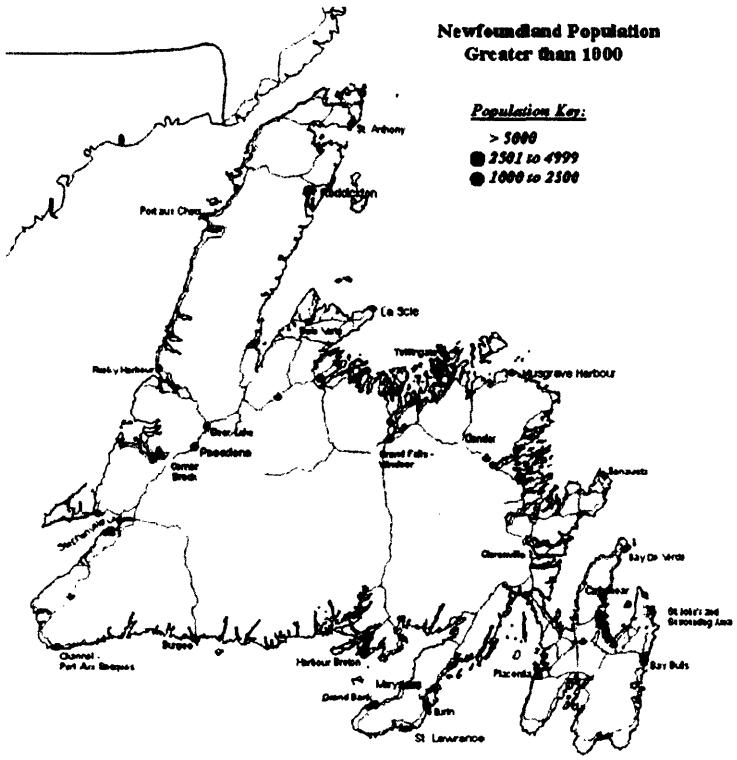


Figure 2: Newfoundland population centers greater than 1000.[87]

Canadian Genome Efforts

Canadian Genome Analysis and Technology Program (CGAT)

Beginning in 1992, Canada "decided to spend C$22 million (US$18 million) over the subsequent five years on research to map and sequence the human genome." C$17 million of funding was to come from the federal government, with C$12 million from the Industry, Science and Technology Canada (ISTC) department and C$5 million from the Medical Research Council (MRC). The rest came from an unsolicited donation from the National Cancer Institute of Canada (NCIC), a private organization.[88]

CGAT, which was headed by Ronald Worton of the University of Toronto and Toronto's Hospital for Sick Children (also head of the Canadian portion of the Human Genome Project), was set up as an organization to fund many smaller projects. By 1994, CGAT had invested C$8.5 million of the C$22 million on projects from yeast DNA sequencing and efforts to speed up sequencing generally to parts of the Human Genome Project itself (sequencing parts of chromosomes 2, 7 and 12).[89] However, by 1996, the ISTC had decided to stop supporting CGAT because of a broader four year Canadian federal budget cutback. MRC offered an additional C$5 million match to help compensate for the shortfall, but only if

other funders were found to contribute C$10 million.[90] This seems to have never happened, and CGAT died on the vine.

Genome Canada

By mid-June 1998, the MRC announced a contribution of $17.5 million towards a much larger initiative called Genome Canada, which was first proposed with a budget of $175 million over five years (it is unclear whether these figures are denominated in U.S. or Canadian dollars).[91] In a document entitled "Genome Canada 1998 Blueprint and Principles", it was proposed to fund the project to the tune of C$500 million, with contributions of C$250 million from Prime Minister Cretien (the same person who had cut CGAT), an additional C$65 million from other federal funding sources, and industry, provincial and voluntary gifts adding up to C$125 million.[92] The government Finance Minister, Paul Martin, came back with a contribution of C$160 million in February 2000,[93] which was enough to get the project off the ground. In 2001, the entire project budget was reported to be C$300 million, though now breakdown of funding sources was listed.[94] In a Genome Canada 2004-2009 Strategic Plan filed in August 2004, the public-private partnership nature of Genome Canada was stressed: "From provincial governments to international charities, from non-profit organizations to more than 70 companies, the power of partnerships has been central to our success to date. We expect that the $375 million invested in Genome Canada so far will result in approximately $850 million of Canadian genomics research, 56% or $475 million provided by partners..."[95] It appears from the existence of the strategic plan and lack of articles stating otherwise that Genome Canada has continued to exist beyond its initial five year funding cycle that ended in 2004.

What does Genome Canada do?

When first proposed, its was stated that:

> Genome Canada's mandate is to coordinate Canadian genomics programs into a network of centers to provide the platform technologies and knowledge required for further research. National research centers will receive from $40 million in year 1 up to $65 million by year 5. Funding of targeted applications will increase annually from $15 million in year 1 to $25 million in year 5. Training of skilled genomics technicians will occur throughout the project's life, with $3 million allotted annually for a training program. Targeted collaborative research and implementation will follow by the year 2004.
>
> In addition to the new funding, genomics researchers in Canada now have access to the Canadian Bioinformatics Resource (CBR; Halifax, Nova Scotia), the world's first gigabyte network.[96]

While the funding amounts may have changed, five centers have been established by 2005: Genome British Columbia in Vancouver; Genome Prairie in Calgary; the Ontario Genomics Institute; Genome

Quebec in Montreal; and Genome Atlantic in Halifax (Nova Scotia). Genome Canada is based in the Canadian capital of Ottawa.[97] These centers evaluate and fund approximately 79 specific projects over a wide range of fields: Development of New Technologies; Bioinformatics; Agriculture; Health (over half the projects); Genomics, Ethics, Environmental, Economic, Legal and Social Issues (GE^3LS); Forestry; Environment; Fisheries; and Science and Technology Platform.[98] Funding decisions for projects happen through various rounds of funding "Competitions."[99] There were also a number of "Approved Platforms" that were to build facilities and infrastructure at select sites throughout the country.[100]

CARTaGENE

CARTaGENE (sometimes written "CART@GENE") is a project in population genetics designed to bank genes from a representative sample of Quebec's population. The goal is to gather genotype and phenotype from between 50,000[101] and 60,000[102] individuals, representing about 1.5% of Quebec's population.

Very little information is available about project's origins, except that in 2000 it was reported that "[t]he FRSQ [Fonds de la recherche en santé du Québec—Quebec health research fund] has recently given the RGMA [Quebec Network of Applied Genetic Medicine] the mandate to develop a large human genetics project over the next 4 years."[103] In spring 2005, the project website (http://www.cartagene.qc.ca) was under construction with all links to it broken. It did promise to reopen on 15 May 2005, and also invited those interested to a CARTaGENE workshop to be held on 13 June 2005. It further suggests that "[t]he project of genomic of the CARTaGENE populations evolved/moved since the last workshop of work of June 11, 2003 and we want to present the last version for discussion and comments before finalizing the request for financing for the autumn."[104] A related site[105] gave the following background and introduction to CARTaGENE:

> The project is directed by Dr. Claude Laberge, President and Director of the Network of Applied Genetic Medicine of Quebec (RMGA). A multidisciplinary team of the RMGA has been working since 1999 on the structure of a new and original project in the area of population genomics, CARTaGENE. Several workshops have been organized in order to obtain constructive feedback from ethicists, policy-makers and the public on the initial project. In light of the comments and concerns voiced during those workshops, the team is currently re-evaluating a certain number of elements (i.e. anonymization, the need for a citizens jury and the non-longitudinal nature of the project).
>
> The CARTaGENE project will consist of: a DNA extraction, storage and management platform; a clinical platform for large-scale human genomics studies; a data centre; and an informatics and data management platform. The Institute for Populations and Genetics (IPEG), a not-for-profit, independent organization, is being created and incorporated to control and manage, in the public interest, major population genetics/genomics/ proteomics projects, including the CARTaGENE

project.

The CARTaGENE project will map genetic variation in a large reference population of Quebec. The CARTaGENE resource will allow large-scale medical, pharmacogenomic and public health studies, including association studies of common diseases or "protective" phenotypes and lead to the discovery of new susceptibility genes. The demographic component of the project will determine mutation frequencies in the different regions of the Province, and thus guide the establishment of health programs of medical genetic services tailored to the needs of the regional sub-populations. Globally, the aim is to provide information for the best use of genetic knowledge and technology in the public health system.

The long-term goal is the constitution of an "international" project for integrated population genomics, as well as the provision of well-matched case-control sub-cohorts for finding genes predisposing to common, complex diseases or phenotypes of interest, particularly for high frequency alleles and so, expand the development of predictive and diagnostic technologies.

CARTaGENE is a modern population genomics project that integrates and exploits the advantages of the existing Canadian health care and legal system, i.e. universal health care, public health care, public health expertise, unique medical identifier numbers, comprehensive health and environmental record linkage with a genealogical/demographic database, extensive privacy and access legislation and a heterogeneous modern population.

Once funding is secured, samples will be randomly collected from 60,000 individuals aged 25-74 over a period of four years.

CARTaGENE is not the only project in population genetics. In fact, many European countries have put in place population banking projects. That kind of project wants to analyze the role of genetic variation in human biologic diversity. Under the aegis of Genome Canada and Genome Quebec, four such public population projects in genomics have agreed to develop integrated partnerships as part of the P3G Consortium (Public Population Project in Genomics) (www.p3gconsortium.org). Finland study of twins involving seven other countries (GenomEUtwin), Estonian Genome Project and the UK Biobank. This Consortium Initiative will allow a project such as CARTaGENE to attain international recognition and contribution to the advancement of genetic knowledge.

Donors give a blood sample as well as personal and family medical histories. CARTaGENE also plans to integrate and access data from the BALSAC Project, a population registry that uses public documents like birth and marriage certificates to piece together family trees. See Canada Appendix B for a brief overview of BALSAC, which contains data "dating back to emigration from France in the 17th century...".[106]

Sources go out of their way to discuss the public nature of CARTaGENE. One states that "[t]he CARTaGENE database will be public property, with no explicit commercial involvement."[107] Another says that the "Quebec DNA [bank does] not intend to have any exclusivity of access for any public or private laboratory. The only restrictions would be based on scientific and institutional review board (IRB) decisions."[108]

Consent, Access and the Legal Climate

CARTaGENE draws "from well-established collections of biological samples, but continue[s] to enroll volunteers and obtain new data."[109] Written consent is necessary according to Canadian law (Personal Information Access Legislation) and the Quebec Civil Code[110]:

> In Canada, current law compels researchers to obtain an informed consent for the use of identifiable health information and tissue for research purposes. Although emerging health information legislation is beginning to alter this general rule, it remains the dominant approach. From the perspective of Canadian courts, health information is closely tied to personal integrity and the notion of autonomy. As such, individuals have an enduring right to control what happens to their identifiable health information.
>
> Existing research ethics policy also requires consent for the use of previously collected tissue. Article 10.3 of the Tri-Council Policy Statement notes: "When identification is possible, researchers shall seek to obtain free and informed consent from individuals, or from their authorized third parties, for the use of the previously collected tissue." The explanatory text accompanying this article explicitly states that it applies to genetic research and notes that "[i]dentification is a matter of sensitivity for individuals, families and members of groups."
>
> In practice, a technical application of existing consent law and research ethics policy would require a new consent for each novel use of an identifiable DNA sample in a databank. As such, Canadian researchers seem likely to face the same practical challenges in the administration of large DNA databanks as outlined by policy-makers in other jurisdictions.[111]

In addition to Canadian law, CARTaGENE is also subject to the "Statement of Principles on the Ethical Conduct of Human Genetic Research Involving Population"[112] as well as the "Statement of Principles: Human Genome Research."[113] The former lays out "ten fundamental principles" that "flow from respect for the inherent dignity of the person": Individuality, Diversity, Complexity, Reciprocity, Solidarity, Security, Accountability, Equity, Citizenry and Universality.

It is not know how the concepts outlined in these two documents are carried out when seeking consent. One commentary suggests that "[v]olunteers participating in the Quebec CARTaGENE project will give a general consent with additional consent for multi-layered options. A general consent will allow the anonymized use of data and biological materials; however, in order to provide benefits to participants from the semi-longitudinal approach, participants will be offered a variety of different choices."[114] On the other hand:

> If volunteers wish to withdraw from the database, or if they need to be recontacted for research and/or consent purposes, their personal information in the databank will need to remain coded and, therefore, cannot be completely anonymized. Under these circumstances, protection of donor confidentiality is usually addressed through the establishment of an independent body that controls the decoding of samples and the distribution of information to authorized researchers.

> Thus, the Quebec CARTaGENE project will be double-coded by the Quebec Health Insurance Board (RAMQ) and by CARTaGENE.[115]

While information regarding the logistic details of this consent process is not readily available, it is important to note the general approach the Quebec has used when working with the community. Once source says that "...Quebec favor[s] a public participation or partnership approach [to interacting with the community] where analysis of public opinion is both quantitative and qualitative."[116] This cooperative, interactive approach was compared favorably against and stood in stark contrast to Iceland and Estonia, which it says favored "a [one-directional, top-down] communication type of approach" and that this communication was based in anticipation of and reaction to quantitative polls. Instead, CARTaGENE "has emphasized the need to treat research subjects as collaborators and participants in the research process rather than as merely the source for biomaterial and medical information...Those involved in the CARTaGENE project are working to engage the community in a research partnership by encouraging an open dialogue among those involved in the project. They have proposed the establishment of a citizen forum to ensure a process of continuous consultation starting before recruitment begins and continuing throughout the research process."[117] This "research partnership" is truly intended to be two-way: RMGA supports a project parallel to CARTaGENE called ECOGENE-21, which "is designed to develop and evaluate resources and strategies for integrating and transferring new knowledge of the human genome [especially from CARTaGENE] to individuals, families and communities."[118]

Genizon/Galileo Genomics

Galileo Genomics was established in March 1999 to exploit the Quebec Founder Population database as a for-profit company with Dr. John Hooper as CEO. In September of that year, the company partnered with Myriad Genetics Inc., who bought 15% of Galileo for $750,000.[119] There were six subsequent financing events: CAD$16.5 million of equity funding on 10 Oct 2001; CAD$6.5 million of equity and debt on 14 Aug 2002; CAD$7.7 million of equity on 25 Feb 2003; CAD$11.15 in equity on 7 Jan 2004; CAD$7 million financing through an Investissement Quebec Loan on 19 Jan 2004; and an additional CAD$11 million of equity on 13 December 2004, when it changed its name to Genizon Biosciences "to reflect addition of gene-to-target capabilities."[120]

In addition to raising money and partnering with companies (Perlegen and First Genetic Trust in addition to Myriad), the company made significant progress researching genes. In June 2004, it announced major discoveries in Crohn's disease. In October of that year, they unveiled a SNP linkage disequilibrium map for the Quebec population. And on 21 April 2005, Genizon announced major progress in understanding

genes associated with psoriasis.[121] The company reports ongoing programs in a wide variety of disease areas, from acne and baldness to glaucoma, panic disorder and schizophrenia.[122]

It appears that Genizon has its own patient recruitment efforts; however, it is not clear how the Genizon biobank shares information with CARTaGENE and vice-versa—or whether they share at all. Also, the consent procedures are not clear, though the website states that "[t]he participation of individuals recruited for one of Genizon's gene discovery programs needs not be limited to that program. All participants for Genizon's programs are given the option to participate in (or opt out of) Genizon's Biobank, for which they provide separate consent. Samples collected into Genizon's Biobank may be used in several gene discovery programs."[123] Genizon reports that it has created an independent Ethics Advisory Committee and that "Genizon respects the confidentiality of all research participants. From the moment of recruitment, a participant is given a code number that may be used for retrieval of all research information associated with that individual in a process called 'denominalization'. Access to the participants' personal information is strictly restricted to recruitment, and code numbers are used for all other data. Research scientists have access only to coded information."[124]

The company states that "[i]n recognition of the contribution to Genizon's research made by the population of Quebec, the company has committed to donate three per cent of its net profits to a foundation for the benefit of Quebecers."[125] Because Genizon remains privately held, it is not clear whether the company is yet profitable.

Newfoundland and Newfound Genomics

Unlike Quebec, there are no public or private plans in Newfoundland to initiate a large gene database.[126] However, beginning in 1998 the province was inundated with groups trying to do studies on the population, many without giving anything back. After a number of years of tolerating "helicopter genetics"[127] by "Texas vampires"—taking blood samples and then disappearing, local leaders decided to impose their own control.[128] They proposed an ethics review board and various restrictions:

> Policies and standards for genetic research had strong support from the minister of Health and Community Services in May 2000. But 5 months later, the premier of Newfoundland, Brian Tobin, unexpectedly resigned, sending provincial politics into a flux from which it has yet to recover.
>
> Since 2000, three premiers have been sworn into office, and [Daryl] Pullman [a bioethicist at Memorial University of Newfoundland] said the educational process can be especially slow because talk of an ethics review board "isn't much of a vote getter," and, with the government running a sizable debt, most politicians wrongly view the panel as expensive.[129]

Yet this November 2004 article suggested that the bill to establish an ethics board was gaining momentum and could come up for vote in spring 2005.

In the midst of this chaos, one company seems to have been visible. Newfound Genomics was first proposed in February 2000 as a joint venture between UK-based Gemini and Newfoundland's Lineage Biomedical.[130] Newfound was incorporated in June of that year.[131] Little information is available on Lineage, though it may have been a one-person company started by Wayne Gulliver, a Newfoundland dermatologist.[132]

Gemini had "established a broad network of collaborators that provide[d] them with access to over 30,000 twins (around 20% being non-identical twins) from diverse ethnic backgrounds (including the UK, Australia and China) and which are not selected for any particular disease. [By August 2000] Gemini [had] already collected and analysed data from over 8,000 twins."[133] The homogenous Newfound population seemed to augment Gemini's twin data.

Though no specific details are available, Gemini's publicly filed financial documents indicate that they "have attempted to ensure that all clinical data and genetic and other biological samples that [Gemini receives] have been collected from volunteers on an anonymous basis and with appropriate consents for purposes which extend to cover our gene discovery programs and other activities...[this occurs] as part of a study that is reviewed by the institutional review board or ethics committee that supervises the hospital or clinic where the collections are taken. In certain studies, an independent review board is consulted." There is also mention about the need for "confidentiality and the appropriate uses of the resulting information."

In return, the region received "expert diagnosis, assessment, and treatment where possible, as well as the creation of jobs and a state-of-the-art genomics and genetics research center. In addition, a 1% 'net royalty' on whatever comes out of the research will go into a charitable trust for the population."

On 29 May 2001, Gemini merged with Sequenom, a former partner.[134] The combined company, under the name Sequenom, is focused on selling their MassARRAY Genetic Analysis System. Newfound Genomics was spun out again by its managers in December 2002 and remains a small company engaged in the same type of research.[135]

Canada Appendix A: Mendelian phenotypes and geographic distribution in Quebec[136]

		Regional distributions	
Disease	**OMIM**	**Ch-SLSJ and probands/cases**	**Other**
Congenital liver fibrosis		+4/4	
Cystic fibrosis	219700	(+)97/114	+[a]
Cystinosis	219800	+7/8	
Cytochrome oxidase defic.	220111	+27/33	
Familial hypercholesterolemia	143890	+	+[b]
Friedreich ataxia	239300		+[c]
Hemochromatosis	235200	+28/54	
Histidinemia	235800	+28/54	
Hyperphenylalaninemia (PKU and non-PKU HPA)	261600	(+)	+[a]
Intestinal atresia (multiple)	243150	+2/2	
Lipoprotein lipase defic.	238600	+22/33	+[d]
Mucolipidosis II	252500	+9/9	
Myotonic dystrophy	160900		
Oculopharyngeal muscular dystrophy	164300		+[c, e]
Polyneuropathy sensorimotor, C=¡ agenesis of corpus callosum	218000	+76/94	
Pseudo-vitamin D deficiency rickets	264700	+36/52	
Sarcosinemia	268900	+21/22	
Spastic ataxia of Charlevoix-Saguenay (ARSACS)	270550	+116/201	
Tay-Sachs disease	272800	(+)	+[f]
β-thalassemia	141900		+[g]
Tyrosinemia type 1	276700	+88/114	
Zellweger syndrome	214100	+5/5	

+ Specific alleles in the region.

[a] Allelic heterogeneity stratifies in Quebec.

[b] Multiple origins.

[c] Southeast Quebec.

[d] Codon 188 and 207 alleles segregate toward western and eastern Quebec regions, respectively.

[e] Southwest Quebec.

[f] Unusual allele in French Canadians (Rimouski region).

[g] β -thalassemia minor alleles in French Canadians (Portneuf County near Quebec City).

BALSAC PROJECT

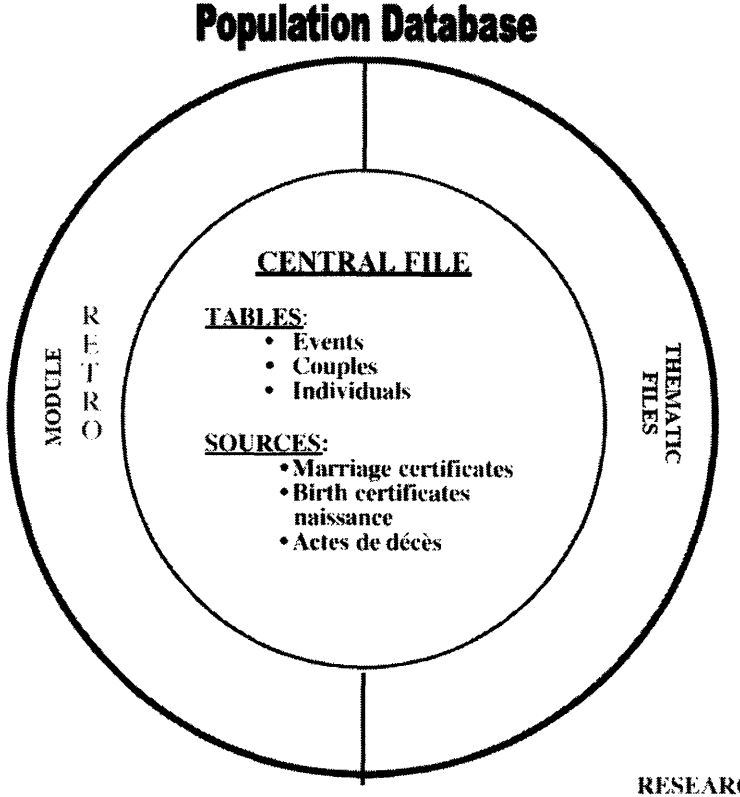
BALSAC POPULATION DATABASE

BALSAC is a computerized database for compiling Quebec family histories and genealogies from the 17th to the 20th centuries. The data are collected from public records (primarily marriage certificates). The database also contains historical, social, cultural and economic information in thematic files. BALSAC'S analytical programs are useful in a wide range of fields from geography to genetic epidemiology. An additional module known as RETRO enables genealogies to be constructed over four centuries.

BALSAC does not include medical or genetic data.

AREAS OF APPLICATION

By its very nature, BALSAC has applications in many fields of study in various disciplines and areas of activity. They include the social sciences (e.g. geography, history, ethnology, sociology and demographics), human population genetics and genetic epidemiology, namely the study of the structure of populations and the related risk of hereditary diseases in particular.



BALSAC Web Site
www.uqac.ca/balsac

SUBJECTS, FIELDS OF RESEARCH

- fertility, marriage, mortality
- literacy
- geographic concentrations of family names
- family biography
- individual biography
- geographic mobility
- social mobility
- population
- family reproduction
- family relationships
- founder effect
- consanguinity, kinship
- genetic diffusion, transmission

PROTECTING PERSONAL INFORMATION

Access to BALSAC and use of the database is controlled and protected through various means:

- legal, legislative
- institutional (internal and external)
- personal, contractual
- technical, computerized
- physical

RESEARCH SERVICES

BALSAC Project, 555 boul. de l'Université
Chicoutimi, Quebec G7H 2B1
Tel.: (418) 545-5517 - Fax: (418) 545-5518
E-mail: balsac@uqac.ca

Université du Québec à Chicoutimi

UNIVERSITÉ LAVAL

McGill

Université de Montréal

(Dernière mise à jour : 2004)

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Estonia & EGeen

About Estonia and its Population

Unlike more isolated populations like those of Iceland and north Sweden, Estonia, located on the Baltic Sea, has a history of struggling for independence—and dominance by its more powerful neighbors. Archeological records of early human dwellers date back to at least 7500 BCE, with the first stable population of Finno-Ugric hunters arriving sometime between 3000 and 2000 BCE.[138] In the 13th century, Germanic princes invaded, followed by many years of being fought over by Lithuanians, Poles, Germanic groups, Prussians, Swedes and Russians. The Estonian gene pool is diverse because of the intermixing of these numerous invaders.

In the late 1800's, the Russians were the unpopular hegemons in the region. However,

> [t]he fight to emerge as an independent nation seemed to have been won in 1920 when Soviet Russia signed a peace treaty with the parliamentary republic of Estonia, recognising its independence in perpetuity. But, caught between the ascendant Soviet Union and expansionist Nazi Germany, Estonia soon lapsed from democracy into authoritarianism, and prime minister Konstantin Päts took over as dictator in 1934.
>
> The Nazi-Soviet non-aggression pact of 1939 secretly placed Estonia under the Soviet sphere of influence and the Soviet authorities began nationalisation and purges that saw up to 60,000 Estonians killed, deported or forced to flee. That's why some Estonians mistakenly saw Adolf Hitler's troops as liberators when they invaded the USSR and occupied the Baltic states in 1941.[139]

Estonia remained under Soviet control from 1944 until its formal declaration of independence in 1991, which was concurrent with the fall of the USSR. Under the Soviets, Estonia had been considered a major center of molecular biology and genetics. Scientists were allowed to train at and spend time in top labs abroad, a rare privilege. Artur Lind started molecular genetics at the University of Tartu in the late 1960's. [140] Tartu, the country's second largest city and home of the country's only medical school, serves as the center of the country's nascent biotech industry.

After the fall of the Soviet Union, Estonia struggled to find a sense of identity as it attempted to re-integrate itself with the rest of the world. Finland's corporate behemoth Nokia is frequently mentioned: Estonia wished for world recognition and leadership in something, and some thought that biotech could be "Estonia's Nokia".[141] While the ultimate success of biotech in Estonia remains to be seen, the country

was able to integrate itself politically and economically with the Western world, joining both the European Union and NATO in 2004.[142]

Today, Estonia has a population of about 1.4 million people, most of whom speak Estonian, though there is a sizeable Russian-speaking minority (30%).[143] Because of the various immigration patterns described above, the gene pool is heterogeneous with a disease profile similar to much of the Western world.[144] Cardiovascular disease, cancer and trauma are the top three causes of death.[145] Life expectancy is 70 year, and family trees can typically be traced back into the 1600's.[146]

Estonia is a relatively poor country with a small economy. Total GDP in 2004 was US$8.4 bn (compare versus Finland: 182.6 bn; Latvia: 12.7 bn; Russia 582.4 bn; Sweden 345.1 bn), with GDP per capita at only US$8,193 (Finland: 35,040; Latvia: 5,469; Russia 4,040; Sweden 38,295).[147] Despite these relatively low numbers, Estonians are well educated and comfortable with technology. They are the most wired country in Europe, with the most computers per capita. All schools have had access to the internet since 2000. And half of Estonians have a cell phone.[148]

In 2001, per capita expenditure on health care was estimated to be US$562, according to WHO. The healthcare system is state-run: just as "...the other 14 countries that were born when the Soviet Union imploded, Estonia was left with a highly centralized and decaying system of health care", which it reformed through various ways to today's "nationwide mandatory health-insurance scheme" (see footnote for many more details).[149] Some critics point to problems of under-funding and suggest that major public health initiatives are still needed to address smoking, drinking and drug use.[150]

Advent of the Estonian Genome Project

"...[I]t was not until 1998 that political circles realized there was gold to mine from the country's science base, launching the Estonian Innovation Programs. The [national government] announced a new national strategy for research and technology—'Knowledge-based Estonia'—and biotechnology was one of five areas of priority for funding. Through this initiative, Estonia's budget for R&D [was to be] increased from 1.6% to 2.0% of gross domestic product within four years."[151]

It was against the background of the controversial Icelandic/deCODE effort—and the hope of Estonian politicians "of becoming world leaders in something for the first time"[152]-- that Estonia made public in October 1999 plans for a very ambitious Estonian Genome Project with the goal of collecting DNA and health questionnaires (see Estonia Appendix E from one million of the country's 1.4 million people within ten years.[153] There was no preexisting gene bank; the large, heterogeneous population was the

asset, and infrastructure was to be build to exploit it. The total cost was originally estimated at between US$90 and 150 million, with private companies expected to cover a sizeable portion through licensing fees. Sample and data collection were to begin in 2001, initially a pilot study with 10,000 participants.

Such a gene bank would be the world's largest. It was often compared to the Icelandic effort. Even though Iceland's gene bank project with deCODE was to cover the country's entire population, the island nation had only 290,000 inhabitants.[154] The characteristics of the population gene pools were also remarkably different. Iceland was touted for its homogeneity, with nearly its entire population descending from a settlement of a few thousand, and who were thereafter quite isolated. As described above, Estonia's population was heterogeneous from years of conquest.

> Earlier, isolated and genetically homogeneous populations—such as the Basque or the Icelanders—were touted as ideal for gene hunting but there is a growing consensus that heterogeneity may be an advantage in complex conditions involving many genes and environmental factors. Population size also matters, explains medical statistician Max Baur of the University of Bonn, Germany. "In many disease models a very large sample of people will be necessary to home in on genes that play a relatively weak role," he says. Baur also points out that it will be critical to compare study results across various populations.[155]

The strength of any gene bank effort in Estonia was to be based on the scale and quality of the resulting database.

The database would be done based on SNP analysis through DNA chip hybridization, while deCODE uses a different method called microsatellites.[156]

Organization & People of the Estonian Genome Center

Estonian Genome Foundation (EGF)

Thirty five doctors, politicians and researchers[157], led by Drs. Jaanus Pikani (a surgeon-politician and CEO of Tartu University Clinics)[158] and Andres Metspalu (professor of biotechnology at the University of Tartu) formed a non-profit institution called the Estonian Genome Foundation (EGF, or *Eesti Geenikeskus*[159] in Estonian), which spearheaded the effort of presenting the Estonian Genome Center plan to the Estonian government and the scientific council at the University of Tartu.[160,161] Dr. Pikani was Chair of the EGF. Dr. Metspalu's precise role in EGF was not known; however, he had been the central figure in the broader Estonian Genome effort and in 2005 served on the Scientific Advisory board to EGPF (see below). See Estonia Appendix C for Dr. Metspalu's *CV*.

Estonian Genome Project Foundation (EGPF)

One source reports that "...the government established the independent, non-profit-making Estonian Genome Project Foundation" (EGPF, or *Eesti Geenivaramu* in Estonian)[162] to create and manage the database. On 24 April 2001, the supervisory board elected Toomas Vilosius, Chairman of the Social Affairs Committee of the Estonian Parliament, as chairman, and established an ethics committee."[163] Another source gave a slightly different take, suggesting (probably erroneously) that EGF is also a part-owner of the Estonian Genome Project Foundation: "The Estonian database will be the property of a non-profit foundation formed by EGF and the Ministry of Health who would create a body with rights to sell access and information."[164] Other sources do not mention EGF as an owner of EGPF—EGF seems to be a group first and foremost to promote and lobby for biotechnology in Estonia.

EGPF was created by an act of parliament called the Human Genes Research Act (HGRA—see below), which went into effect on January 8, 2001. In addition to establishing the broader legal, ethical and regulatory framework for the genome project effort, HGRA charged EGPF with the task of creating and managing the database and has "'the right to possess, use and dispose' of [tissue samples and health data] under the conditions defined by the HGRA"[165]—making it "the engine of the venture"[166]. An early source reported that "Estonia [presumably via EGPF] plans to strike limited, nonexclusive deals that would, for example, allow a company to mine the database for clues to one or more diseases and receive intellectual property rights to treatments derived from its research. Access to data would be given to public researchers at no cost or for a handling fee."[167]

EGPF was to be financed mostly by private funding (see EGeen below). For example, the pilot project of approximately 10,000 participants was expected to cost 43 million kroons (EUR 2.75 m). While EGeen was expected to cover most of this, "the Estonian Technology Agency of Enterprise Estonia also issued a long-term loan to the Genome Project totaling 4 million kroons or a 256,000 EUR."[168]

As noted above the entire project of 1 million people was estimated to cost between US$90 and 150 million. This estimated cost is similar to the nearly US$160 million raised by deCODE in a July 2000 stock offering, near the peak of the NASDAQ.[169]

EGeen

Though mentioned, non-exclusive licensing never came to fruition. Instead EGeen, a for-profit private US company based in the San Francisco area with an Estonian subsidiary and founded in 2000, was established "to finance the project and commercialize [the Estonian Genome Project's] results via drug and diagnostic target discovery."[170] Andres Metspalu was EGeen's Chief Scientific Officer and Kalev Kask its CEO[171].

Thus was established a public-private partnership, whereby EGeen was to provide significant private sector funding for and return a portion of profits back to EGPF. In exchange, EGeen was the "exclusive commercial licensee of the database...hold[ing] exclusive rights to money-making ventures that rely on the data for the next twenty five years."[172] EGeen's business model seems to involve seeking out partnerships with biotech and pharma firms and sublicensing around specific projects, thus making money through business development by being an intermediary that slices and markets the Estonian Genome Project database.

EGeen announced its first capital infusion in April 2002, a $2.0 million private placement led by SEAF CEE Growth Fund (US$1.1 million) and The Baltics Small Equity Fund (US$0.4 million).[173] "Co-investors include[d] Steve Jurvetson, managing director of a venture capital firm Draper Fisher Jurvetson, and Ned Olivier, founding General Partner of Oxford Bioscience Partners, a leading life science venture capital firm." "Agreements regulating the implementation and financing of the new project were signed on December 31, 2001. In accordance with the agreement, EGeen has made the first of five payments for the pilot study"[174] of 10,000 persons, which began in early September 2002.[175]

A US$4.25 million first round of venture financing was closed on 18 November 2002. Investors included Draper Fisher Jurvetson ePlanet Ventures, Biobank Technology Ventures and Small Enterprise Assistance Funds. In the press release, EGeen said they would "use the funding to continue building the Estonian Gene Bank Foundation database and to expand its related commercial activities.[176]

Privacy and the Human Genes Research Act

The Human Genes Research Act (HGRA) in one fell swoop established the legal, ethical and regulatory groundwork for the Estonian Genome project. It spanned 36 paragraphs[177] on 16 pages[178] and saw widespread support from both politicians and the populace. There were only small pockets of opposition

to the effort, especially from a professor at the University of Tallinn named Tiina Tasmuth. Though her initial objections were ostensibly related to how medical resources in the country were allocated ("With an underfunded health care ...we should not enter into expensive high-tech endeavors."[179]), the title and content of a later article entitled "The Estonian Gene Bank Project—an overt business plan"[180] seemed to belie the author's true objection of making money from population research. With popular support at 90%, the bill was voted into law in parliament on 13 December 2000 by a vote of 42 in favor to only three opposed[181], and took force on January 8, 2001.[182]

Scope of HGRA

> The purpose of the law is to organize genetic research and to establish a gene database. Both these goals shall be achieved while protecting the legitimate interests of the gene donors. The government hopes to prevent misuse of data, discrimination and unauthorized publication of data by means of regulations governing the flow of information between those involved in human gene research. The law also stipulates the conditions for collecting, publishing, evaluating or destroying genetic data. A central foundation for gene research, called Chief Processor [power given to the EGPF], will be established. The Chief Processor will be a non-profit organization under the control of a supervisory board, which will be responsible for collecting, preserving and filing data material, and for coding, publishing or destroying it.
>
> The Chief Processor will have the right to conduct research itself using the data material, or to authorize third parties to do so. The Chief Processor will store various kinds of data, ranging from tissue samples or descriptions of DNA from volunteer donors, to descriptions of the donors' health status and their genealogy in a gene bank to be established by the Chief Processor. However, the results of mandatory genetic testing provided for by law, for example to identify a particular person, may not be stored in the gene bank.
>
> As a general rule - ie in the case of volunteer donors -- the Chief Processor will take a sample of tissue [50 ml of venous blood, from which 1 mg of DNA is extracted and stored in liquid nitrogen] and question donors about their family history and their health status. [The tissue collection and history taking were delegated to properly-trained practicing physicians.] The data obtained will then be encrypted, using a code known only to the Chief Processor. In the coded form, the information may then be disclosed in the form of summarised data records grouping five anonymous gene donors at a time. Ownership of the data passes to the Chief Processor. [That is, the donor no longer owns their data, though they retain certain control and access to it:] The gene donor retains the option of using the data, for example for genetic counselling. As well as the right not to receive details on their own data; donors themselves are also entitled to have the data required for coding and decoding to be destroyed or, if their identity has been unlawfully disclosed, to have the data itself destroyed.
>
> The data stored in the gene bank may only be used by the Chief Processor for the purpose of scientific research, for research into, and treatment of, illnesses, or for statistical purposes. Use of the gene bank for other purposes will not be permitted, for example in civil or criminal proceedings, or for surveillance purposes. The Chief Processor is permitted to delegate its tasks to particular "authorized processors" with the exception of the process of coding and decoding the data. Under the terms of the law, an "authorized processor" may be any natural person or civil--

law entity or an Estonian state agency. The specific requirements for such agencies will be established by the Estonian government. In addition, the Chief Processor may disclose data stored in the gene bank to genetic researchers "for a charge or free of charge".

The legal definition of genetic researchers in this context encompasses all natural persons or civil-law entities, or state or local authorities which engage in genetic research. The setting up of a Data Protection Supervision Authority and an Ethics Committee - which will be specially convened for such cases - are intended to ensure that the legal regulations are adhered to. The law makes further provision for complaints, although this only applies to employment law and insurance law cases. [183]

Main provisions of the Act directly relevant to the patient include: [184]

· The Gene Bank may be used only for scientific research, research into and treatment of illnesses of gene donors, public health research and statistical purposes.

· Only a gene donor and a doctor treating the gene donor shall have the right to receive personalised information.

· Blood samples and health and genetic data are the property of the Gene Bank. A gene donor shall not receive any remuneration for their processing.

· People shall be given an opportunity to participate in the Genome Project, but no one shall be obliged to participate. In order to make a person's self-realisation really free, he or she should be aware of his or her rights and obligations as a gene donor. Therefore, the law stipulates the circumstances of which a gene donor should be notified before his or her blood sample is taken (e.g. how a blood sample is taken, what is done with it, what data can be received from a blood sample, etc.). Only after that, a person can give a valid consent to becoming a gene donor.

· To ensure confidentiality of a gene donor, the personal data of the gene donor shall be separated from genetic data and each blood sample and set of health data shall be given a unique 16-digit code. It is prohibited to connect the database of the Gene Bank to the Internet.

· No one shall be discriminated against on the basis of genetic information.

· A gene donor shall decide whether he or she wants to know his or her genetic data or not.

· If a gene donor does not want to participate in the Genome Project anymore, he or she shall have the

right to demand deletion of the data that enable identification of his or her person or, in certain cases, of all the information stored in the Gene Bank about him or her. After deletion of the given data, it will not be possible to associate a blood sample and a gene donor and the donor shall never receive any information about him or her.

· The law stipulates bringing up criminal charges for inducing a person to become a gene donor, carrying out illegal human research, disclosure of secret information and discrimination.

Furthermore, the act purposely excludes data gained from other non-voluntary genetic tests, such as from a criminal case, from forensic evidence, or through coercion, payment, or "social pressure". Violations of this are punishable by a one year prison term, and researchers who work without patient consent are subject to three years in prison.[185] Patients are also able to "ban access to one's own genetic family tree and on comparing personal data with parents or relatives."

Consent is reach through a written consent form. See Estonia Appendix B for a translated copy of this consent form and related information provided to the patient. The consent form is important because it is required to opt in to the database—no one is included without a consent form. This differs greatly from the much criticized system used by Iceland/deCODE, where the entire population was automatically included in the study unless an individual expressly opted out. The Estonians learned from the Icelander's mistakes and designed a better system. The resulting Human Genes Research Act was ultimately recognized as "[a] commendable law…in that it attempts to summarise the majority of the legal relationships which exist in the field of genetic research in one standard law."[186]

Results

The project received some criticism in addition to that mentioned earlier. Some suggested that "the 'paternalistic tradition' of the postcommunist Baltic states makes it difficult to ensure that informed consent and nondirective counseling of individuals are carried out properly"[187]. Others suggested deceit, in that the publicly touted concept of a "personal gene card/map is a small but important part of a myth created in order to persuade Estonians that their health is going to be vastly improved, with the help of a gene card they can start queuing up for now", even though such a direct, personal benefit, if even possible, would be many years away.[188] As described earlier, the commercial nature of the project was also criticized. Tiina Tasmuth implied that the first generation of informed consent forms made no mention of the fact that "tissue donations may have some commercial value, and that [Estonians'] anonymous data may be commercially exploited."[189]

But despite these islands of criticism, the public remained squarely behind the program, with over 90% support as reported earlier. When asked in a subsequent poll asked their willingness to participate personally in the project, 43% were willing to do so immediately, with 37% undecided but wanting more information. Only 6% were against participating.[190]

In August of 2001, after the NASDAQ crash, the first signs of financial difficulty became apparent when it was reported that "[t]he [pilot study] collection of genetic data from 10,000 Estonians will not be starting this fall as originally planned, and will be delayed until at least Feb. 2002 due to red tape and difficulties with raising the necessary financing."[191] As mentioned earlier, though, EGeen was funded with US$2.0 million in April 2002, which allowed the pilot study to begin in September 2002. By December 2002, "Professor Andres Metspalu [said the pilot study had]...gone well enough to enable it to be extended to the whole country earlier than planned."[192]

Between 2002 and 2003 EGeen was able to sign three partnership deals to study the pharmacogenomics of depression and hypertension.[193] However, in January 2004 the relationship with EGeen began to unravel as "EGeen investors have stopped funding, wishing for a change in the project's aims". Some speculated that the investors would rather focus on specific diseases than build a genome project from the ground up.[194] Though EGeen subsequently funded EGPF with a small additional amount, this disagreement over project aims was the beginning of the end of the public-private partnership.

After funding was cut, the project seems to have fallen apart. In February 2004, Pikani and Metspalu, both board members of EGeen, resigned due to conflicts with the CEO.[195] In April of that year, EGPF CEO Krista Kruuv resigned[196], and in December EGPF and EGeen formally parted ways.[197] Despite having lowered their target from 1 million to 100,000 participants, EGPF seems to have been unable to find additional funding. It announced that it "has only 10 percent of the budget required for 2005...[and] needs in 2005-2007 additional funds of 125 million kroons (EUR 8 mln)." If conditions did not change, it would begin laying off employees in late February 2004.[198]

EGeen lives on and looks to have remade itself as a Clinical Development/Contract Research Organization with the recent "addition of physician's networks and geographical expansion from Estonia to the other Baltic States and Ukraine."[199]

Conclusion

Despite strong popular support, a model legal and ethical framework, and leaders eager to build "Estonian's Nokia", the project seems to have failed due to lack of funding.

Estonia Appendix C: Andres Metspalu *CURRICULUM VITAE*[200]

Full name		**ANDRES METSPALU**
Full postal address		
	Home	65 Kalevi St., Tartu 50103, Estonia
	Office	Tartu University Institute of Molecular and Cell Biology Estonian Biocentre 23 Riia St. Tartu 51010 Estonia
E-mail address		andres@ebc.ee
Telephone numbers		
	Home	+ 372 7 343 256
	Office	+ 372 7 375 029
	GSM	+ 372 5 331 9020
Date of birth		March 11, 1951
Sex		Male
Nationality		Estonian
Knowledge of languages		Estonian – mother tongue English – thorough knowledge Russian – satisfactory knowledge French – learning
Title of degree & awarding institution		Ph.D. in Molecular Biology, Structure and function of the Eukaryotic ribosome, Institute of Molecular Genetics, Ukrainian Acad. Of Sciences, Kiev
Date of award of degree		1979

Professional History

1976	M.D., Tartu University (physician)
1979	Ph.D., in Molecular Biology
1981 – 1982	IREX fellow at Columbia University, New York, USA.
1982	IREX fellow at Yale University, New Haven, USA.
1982 – 1985	Senior scientist at the Laboratory of Molecular Biology, Tartu University.
1985	European Molecular Biology Laboratory (EMBL), Heidelberg, Germany. Two month fellowship from European Society of Biochemistry (FEBS)
1985 – 1992	Head of Laboratory of Gene Expression, Tartu University
1988	Max-Planck Institute of Molecular Genetics, West-Berlin, Germany. One month fellowship from European Molecular Biology Organization (EMBO)
1986 – 1992	Research Director of the Estonian Biocentre.
1991	FEBS (Federation of the European Societies of Biochemistry) Advanced Course, Patras, Greece. "Application of DNA Methods for the Diagnosis of Human Disease". FEBS fellowship.
1991	Visiting scientist at University of Tampere, Finland
1991 – 1992	Visiting scientist at Hamburg University, Dept. of Molecular Biology, Germany. Two months fellowship from DAAD.
1993	Three months research grant from EEC at University of Hamburg, H. Pette Institute for Experimental Immunology.
1993 –1994	Sabbatical leave, visiting professor at Baylor College of Medicine, Dept. of Molecular and Human Genetics with Prof. C.T. Caskey.
1999 – ...	Asper Biotech Ltd., Tartu, Estonia. Founder and Chairman of the Board
1996 – ..	Second appointment as Head of Molecular Diagnostics Centre at Tartu University Clinics
1999- ...	Founder and scientific advisor of the Estonian Genome Project (www.geenivaramu.ee)
2000	WHO International Agency for Research of Cancer (IARC), Lyon, France, The Visiting Scientist Award for 12 months
From 1992	Professor of Biotechnology at University of Tartu, from 2004 this is a permanent position
2004 - ...	Estonian Genome Project, Member of the Management Board

Scientific Boards and Professional Societies

1988 – 1990	Member of the Expert Council of Soviet Union Human Genome program
1994 – ...	Member of European Society of Human Genetics, from 2000 as a board member, from 2004 President-Elect
1995 – ...	Member of American Society of Human Genetics (ASHG)
1995 – ...	Member of The Human Genome Organization (HUGO)
1996 – 2001	Member of Tartu University Council
1997 – 2000 and 2003 – 2006	Member of Estonian Council of Scientific Competence (advisory body for ministry of education and research for science policy and funding)
1999 – ...	Founder, member and member of the board of the Estonian Society of Human Genetics
2001 – 2005	European Science Foundation Functional Genomics Program: Member of steering committee
2003 – 2006	International Congress of Genetics (Brisbane, Australia) member of the SPC.
2003 – ...	Biotechnology Centre of Excellence, Vilnius, Lithuania, Member of the International Board
2003 – ...	Journal "Heredity Cancer in Clinical Practice" editorial board member
1999	Founder and the member of the council of the Estonian Genome Cenre Foundation
2004	P3G Founder and Director

International Scientific Review Boards

2002-2004	The Wellcome Trust, UK
2000	Helmholtz Society, Germany
2001-2003	French Ministry of Research, France

EU Grants

1995 – 1997	EU PECO grant #ERBCIPDCT940260
1995 – 1996	EU PECO grant #ERBCIPDCT940220
1995 – 1997	EU COPERNICUS grant #ERBCIPACT940148
1998 – 2000	EC INCO-COPERNICUS #IC15-CT98-0305
1998 – 2000	EC INCO-COPERNICUS #IC15-CT98-0309
2001 – 2003	EC 5 Framework Programme grant #QLG1-2000-00619
2002 – 2004	EC 5 Framework Programme grant #QLRT-2001-00182

2001 – 2002	European Science Foundation grant, part of ESF Programme on Integrated Approach for Functional Genomics
2004 – 2006	EC 6 Framework Programme grant, proposal # 503155
2004 – 2006	EC 6 Framework Programme grant, proposal # 503243
2004 – 2007	EC, Public Health Programme grant # 2003220

Honours

1980	Soviet Estonian Prize for Sciences
1999	"Man of the Year in Estonia" from "Loop" magazine
2001	3rd Class Order of the Estonian Red Cross
2002	Prix de la Garantie Medicale et Chirurgicale, France
2003	Estonian Science Prize in Medicine
2003	L'Ordre des Palmes Académiques, Chevalier, France

Invited lectures

About 20 invited lectures per year in recent years.

Few selected lectures:

1. 17th International Congress of Clinical Chemistry and Laboratory Medicine, Firenze, Italy, 6th – 11th of June, 1999.
2. Drug Discovery, Improve productivity by integrating novel research and emerging technologies, Cannes, France, 6th –7th of December 2000.
3. 10th International Congress of Human Genetics, Vienna, Austria 15th-19th of May 2001.
4. COGENE: Co-ordination of Genomes Research across Europe, Limassol, Cypros, 17th – 19th of October, 2002.
5. 11th North American ISSX Meeting, Orlando, USA, 27th – 31st of October 2002.
6. Cold Spring Harbor Laboratory/The Wellcome Trust Conference, Hinxton, UK, 24th – 28th of September 2003.
7. European Human Genetics Conference 2003, Birmingham, UK, 3rd – 6th of May, 2003.
8. Days of Molecular Medicine 2004, The Wellcome Trust Conference, Cambridgeshire, UK, 18th – 20th of March 2004.

Publications

About 60 papers in international journals

Few recent publications (full list at: www.biotech.ebc.ee):

1. **Metspalu, A**. "Microarrays and Single Nucleotide Polymorphism (SNP) genotyping". In: **Nature Encyclopedia of the Human Genome**. Nature Publishing Group. 2003. pp. 921-925.
2. Dawson E, Abecasis GR, Bumpstead S, Chen Y, Hunt S, Beare DM, Pabial J, Dibling T, Tinsley E, Kirby S, Carter D, Papaspyridonos M, Livingstone S, Ganske R, Lõhmussaar E, Zernant J, Tõnisson N, Remm M, Mägi R, Puurand T, Vilo J, Kurg A, Rice K, Deloukas P, Mott R, **Metspalu A**, Bentley DR, Cardon LR, Dunham I "A First-Generation Linkage Disequilibrium Map of Human Chromosome 22" **Nature** 418 (2002), 544 – 548.
3. Neeme Tõnisson, Jana Zernant, Ants Kurg, Hendrik Pavel, Georg Slavin, Hanno Roomere, Aune Meiel, Pierre Hainaut and **Andres Metspalu**, "Evaluating the arrayed primer extension resequencing assay of TP53 tumor suppressor gene.", **Proc. Natl. Acad. Sci.** USA, 2002, Vol. 99, Issue 8, 5503-5508.

Other

Member of the Tartu Rotary Club

Member of the Sailing Club "Kalev"

Second marriage, four children.

Estonia Appendix D: Gene Donor Consent Form[201]

Annex 1
Regulation No 125, Dec 17, 2001
Minister of Social Affairs

GENE DONOR CONSENT FORM

This document contains essential information about the rights of a gene donor in order to help me decide whether to become a gene donor. The Human Genes Research Act regulates the rights of gene donors. Further information about becoming and being a gene donor is given in the gene donor information kit. This consent form, the law and information kit shall be explained to me by a specialist and I may ask questions at any time.

I have been informed and I am aware of the following:

1) The aim of the Estonian Genome Project Foundation is to establish the Gene Bank, a database that contains health and gene data of the people of Estonia. The Gene Bank enables scientific and applied gene and health research to be carried out in order to find genes that influence the development of illnesses. Research carried out with the help of the Gene Bank shall not be limited to the present scientific level.
2) My consent to become a gene donor is entirely voluntary. No one may discriminate against me on the basis of being or not being a gene donor. No one may force me to become a gene donor.
3) I may not request a fee for providing a tissue sample, for describing my state of health or genealogy, or for the use of my research results. I am aware of the fact that my tissue sample may have some commercial value and that commercial entities may receive anonymous data about gene donors. The right of ownership of the tissue sample, of the description of my state of health and of other personal data and genealogy shall be transferred to the Estonian Genome Project Foundation. The foundation has been established and it is controlled by the Republic of Estonia. The foundation is financed by commercial entities.
4) If I wish, I may submit additional information on myself to the Estonian Genome Project Foundation. The Estonian Genome Project Foundation has the right to receive information about my state of health from other databases. I have the right to prohibit the supplementation, updating and verification of descriptions of my state of health stored in the Gene Bank.
5) Data on hereditary characteristics and genetic risks obtained as a result of genetic research may be unpleasant for me. I have the right to not know my genetic data.
6) I have the right to know my genetic data and other data about me stored in the Gene Bank, except my genealogy. I have the right to genetic counseling upon accessing my data stored in the Gene Bank. I can access my data stored in the Gene Bank free of charge.
7) No one has the right to access my data stored in the Gene Bank if the data have been decoded. I may grant consent to my doctor to access my decoded data contained in the Gene Bank. Decoding is performed by the Estonian Genome Project Foundation in cases and pursuant to procedure provided by law.
8) The Estonian Genome Project Foundation may issue tissue samples, descriptions of DNA and descriptions of the state of health from the Gene Bank only in coded form so that the identity of the gene donor remains unknown to the receiver.
9) I have the right to apply at any time to the Estonian Genome Project Foundation for the destruction of my data that can be decoded. Upon unlawful disclosure of my identity, I have the right to claim compensation for damage and apply to the Estonian Genome Project Foundation for the destruction of my tissue sample, description of DNA and description of my state of health.
10) I can withdraw my consent to become a gene donor until my tissue sample or the description of my state of health is coded.

By signing this document, I give my free and informed consent to:

1) Become a gene donor;
2) Provide a 50 ml venous blood sample from my arm using single-use equipment;
3) Have a description of my state of health and genealogy prepared;
4) Enter the tissue sample, description of mu state of health and my genealogy in the Gene Bank in coded form;
5) The use thereof for genetic research, public health research and statistical purposes in conformity with the law.

A copy of this consent form remains with me.

Gene donor

Full name: _____
ID Code or Date of Birth _____
Sex _____
Place of Residence: _____

Legal representative

Full name: _____
ID Code or Date of Birth _____
Sex _____
Place of Residence _____

Date: _____

Signature: _____

Information concerning the health service provider who is to take the tissue sample:

Information about the Gene Donor Consent Form

This information letter explains the Gene Donor Consent Form in detail and it helps to better understand the aspects related to the Estonian Genome Project.
Becoming a gene donor is voluntary.

Estonian Genome Project

The aim of the Estonian Genome Project is to establish a Gene Bank, a database that contains health and genetic data on the people of Estonia.
The Gene Bank enables gene and health research to be carried out in order to find genes that influence the development of illnesses.
The Gene Bank is established and run by the Estonian Genome Project Foundation (EGPF) established and controlled by the Republic of Estonia.

Human Genes Research Act

Establishment and upkeep of the Gene Bank is regulated by the Human Genes Research Act.
The law regulates the rights and obligations of a gene donor, the rules of data protection and other securities for protection of the rights of a gene donor.

Definitions:

· Gene donor means a person who provides a tissue sample for the purposes of genetic research and with regard to whom a description of the state of health and genealogy are prepared.
· Tissue sample is 50 ml of venous blood of a gene donor. The tissue sample is taken by a doctor or a nurse. In a laboratory of the EGPF, DNA containing genetic information is separated.
· DNA is a substance carrying genetic information.
· Genetic data are a description of DNA.
· Description of state of health means data collected for use in genetic research which reflects the state of health of a gene donor, illnesses he or she has suffered from and treatment thereof, and his or her lifestyle. The description of the state of health is prepared by asking the gene donor questions and by relying on the data of hospitals and illness registers. In addition, questions are asked about the illnesses and habits appearing in the family of the gene donor, but no specific persons or generations are identified.
· Genealogy is prepared about the blood relatives of a gene donor. The purpose of preparing genealogy is to discover connections between illnesses and genetic peculiarities in different generations. The Gene Bank does not reveal any information about the relatives of a gene donor.

Why is the Gene Bank established?

By analysing the health, genealogy and genetic data gathered to the Gene Bank, genes connected to one or another illness can be found.
The Gene Bank provides a gene donor with an opportunity to assess his or her health risks and diagnose illnesses more precisely, prevent falling ill and receive more effective treatment in the future. The establishment of the Gene Bank is a long-term process. The above opportunities enable scientific research and discoveries, and application and development of new technologies to be carried out.

Establishment of the Gene Bank

The description of the state of health status is prepared and a tissue sample is taken by the family doctor of the gene donor, who sends them to the EGPF. A copy of the collected description of the state of health remains with the family doctors for usage in daily treatment.
In order for the information concerning the gene donor to be as precise as possible, the EGPF compares the description of the state of health with the data of other databases. After that, the description of the state of health is coded and entered into the Gene Bank.
The tissue sample is coded and in a laboratory, the DNA is separated from it. Next, a DNA description, which is preserved electronically, is prepared.
In addition, the genealogy of the gene donor is prepared in the Gene Bank.
The written consent of the gene donor is preserved in a separate archive in the Gene Bank.
The Gene Bank is constantly supplemented.

What is coding?

Coding means the replacement with a unique code of such data (name and personal identification code), which enables the direct identification of the person.
The code has 16 digits and it is created by a computer by using incidental numbers and letters. The code is adhered to the Consent Form.
Coding is one of the security measures for protection of the data. The Data Protection Inspectorate supervises conformity with all data protection rules.

Who can get data from the Gene Bank?

Only the gene donor himself or herself can get data about a specific gene donor from the Gene Bank, and upon his or her consent, his or her doctor.
Scientists can get only anonymous data.
The anonymous data of the Gene Bank can be issued for scientific research purposes abroad as well.
For example, the police, the prosecutor's office, the court, the health insurance fund or insurance companies cannot get any data from the Gene Bank. No data are given to family members or relatives of the gene donor.

How are the data issued from the Gene Bank?

The Gene Bank issued descriptions of states of health and genetic data in a coded form.
The data that enable direct identification of the gene donor are not issued. In order to prevent indirect identification of the gene donor, the data of at least five anonymous gene donors are issued at a time.
The gene donor or his or her doctor is issued a description of the state of health and genetic data upon the written application of the gene donor.

What is done with the data?

The data of the Gene Bank are used for scientific research in the fields of health of people and genetics.
The purpose of the research is to find genes influencing formation and development of illnesses.
The data of the Gene Bank must not be used for identification of paternity and persons or upon criminal investigation.

How is discrimination excluded?

The law clearly prohibits discrimination and stipulates a penalty.
Pursuant to the Criminal Code, unlawful restriction of the rights of a person or conferral of unlawful preferences on a person based on the genetic risks of the person is punishable by a fine, detention or up to one year imprisonment.
The rights of the gene donor are not restricted and no preferences are conferred on the gene donor. Becoming a gene donor is a secret that the EGPF is prohibited from revealing. Insurance companies and employers are prohibited from collecting genetic personal data about policyholders or employees.
The Labour Inspectorate and the Insurance Supervision Authority shall solve related complaints.

What is decoding?

Decoding is reverse identification of the gene donor.
Decoding enables association of the gene donor with a description of the state of health and genetic data.
Decoding can be performed only by the EGPF and in cases stipulated by law.
It is permitted to decode data only for the following purposes:
· issuance of the data to the gene donor;
· issuance of the data to the doctor of the gene donor;
· renewal, supplementation and verification of data;
· asking the gene donor for new data upon the consent of the Ethics Committee;
· taking a new tissue sample upon the consent of the gene donor;
· supplementation of genealogy;
· destruction of data entered into the Gene Bank.

Who owns the Gene Bank?

The Gene Bank, i.e. all the data entered into the Gene Bank, belongs to the EGPF.
Tissue samples, the Gene Donor Consent Form and data that are not protected with a code are not transferable (they cannot be sold or presented, etc).

Funding of the EGPF

The Government of the Republic of Estonia supported initiation of the EGPF. The establishment of the Gene Bank is funded by investors and funds that are interested in making scientific and applied discoveries in the field of medicine and genetics and later, if results are successful, making profit.
The gene donor does not have the right to receive a share of the income of the investors, funds and the EGPF.
The gene donor does not receive money for giving a tissue sample, description of state of health or preparation and research of the genealogy and usage of the research results.
The data of the gene donor are kept in the Gene Bank free of charge.
The gene donor can access his or her data free of charge.

What are the rights of the gene donor?
· A gene donor has the right to access his or her data stored in the Gene Bank, except his or her genealogy. Upon consent of the gene donor, his or her attending physician can receive data from the Gene Bank.
· A gene donor has the right to genetic counselling upon accessing his or her data stored in the Gene Bank. Data on hereditary characteristics and genetic risks obtained as a result of genetic research may be unpleasant for the gene donor.
· A gene donor has the right not to know his or her genetic data.
· A gene donor has the right to reveal the fact of being or not being a gene donor.
· A gene donor has the right to present additional data about him- or herself to the EGPF through his or her family doctor.
· A gene donor has the right to prohibit the supplementation, updating or verification of descriptions of his or her state of health stored in the Gene Bank. Until that moment, the EGPF can receive data about the state of health of the gene donor from other databases.
· A gene donor has the right to apply for destruction of the data enabling decoding after which it is not possible to identify the person of the gene donor anymore. After that, the gene donor or his or her doctor will never receive any genetic data about the gene donor. Thus, it is not possible to learn which data are kept in the Gene Bank about the specific gene donor.
· If the person of the gene donor is revealed illegally, the gene donor can apply for destruction of all the data and the tissue sample collected about him or her in the Gene Bank. The destruction obligation also applies to other people who have data originating from the Gene Bank.
· A gene donor has the right to withdraw his or her consent until coding of the tissue sample or health data. In such case, the data will not reach the Gene Bank. After coding, the gene donor has the right to demand destruction of the data enabling decoding.

Consent of the gene donor

People interested in becoming a gene donor should address their family doctor. Important circumstances are explained and the Gene Donor Consent Form and this newsletter are introduced to them.
A person who wants to become a gene donor signs the Consent Form after which his or her description of the state of health is prepared and a tissue sample taken.
Protection of the rights of gene donors connected to the establishment of the Gene Bank and an independent Ethics Committee of the EGPF monitors adherence to the ethical norms.

Estonia Appendix E: Introduction of the Estonian Gene Bank's Questionnaire of the State of Health and Genealogy

The state of health and genealogy data collected through the questionnaire of the Estonian Gene Bank is needed for further genetic research.
The questionnaire is longer and more thorough than this introduction. This brochure contains only the questions in case of which you might need some more time to think. Your family doctor has probably already asked some of these questions in order to offer you better consultation and treatment.
The data collected is necessary in the everyday work of your family doctor as it helps the doctor to better understand your health problems. A copy of the completed questionnaire will remain with your family doctor.
We would ask you to write down some data before your visit to the doctor, so that filling in the questionnaire goes more smoothly. You can make notes in this brochure of introduction of the questionnaire. It would be better if you have examined other information before offered by the Gene Bank, especially the Gene Donor Consent Form and the newsletter.

Personal data

Personal data is stored in coded form in a separate database. Storing the personal data is needed especially if you wish to exercise your lawful right to use your genetic data.
Personal data contains your first name and surname, sex, date of birth, ID code and place of residence. If your surname has changed, please note your previous surnames.

Genealogy

Genealogy is used for the organisation of genetic data. It is not possible to examine the data about genealogy stored in the Gene Bank, as the Human Gene Research Act does not allow it. The aim of the Act is to guarantee the privacy of a gene donor's personal life.
While compiling the genealogy, your family doctor will ask information about your mother, father, their children, as well as your grandparents and your children. As the presence of twins is essential information for scientists in the scientific research following the collection of data, there is a respective question about sisters and brothers and children born on the same date.
In case of children up to the age of 18, there is also a question about diseases they have suffered from. If the child is 7 years old or older, you should inform your child that you are going to give information about his or her diseases. Genealogy shall be compiled only about blood relatives.

Mother

First name	
Surname	
Maiden name	

Date of birth	
Date of death	
Reason of death	

Father

First name	
Surname	
Surname at birth	
Date of birth	
Date of death	
Reason of death	

Mother's children

Full name			
Date of birth			
Date of death			
Reason of death			
Twins			

Father's children

Full name			
Date of birth			
Date of death			
Reason of death			
Twins			

Father's father

Full name	
Date of birth	
Date of death	
Reason of death	

Father's mother

Full name	
Date of birth	
Date of death	
Reason of death	

Mother's father

Full name	
Date of birth	
Date of death	
Reason of death	

Mother's mother

Full name	
Date of birth	
Date of death	
Reason of death	

Your children

Full name			
Sex			
Date of birth			
Date of death			
Diseases suffered from (in case of children under 18 years)			
Twins			

Description of the state of health

The description of the state of health contains questions about education, employment, physical activity, nutrition habits, general health condition, smoking and alcohol consumption. Women should answer the questions about hormonal contraceptive preparations and menopause medicaments, and pregnancies. There is a different part about diseases suffered and medicaments used. There are also questions about your nationality and native language. In determining the nationality, you should know your parents', grandparents' and great grandparents' nationality.

Employment

Present occupation	
Occupation held for the longest time during your life (main occupation)	
Beginning of employment at the main occupation	
End of employment at the main occupation	

Please describe your physical effort at the main occupation.

Mainly sedentary	
Mainly standing or walking without special physical effort	
Mainly standing or walking with special physical effort	
The occupation needs much physical effort	

Physical activity

Please answer how many hours a week you spend on the following activities.

Quick walking	
Moderate walking	
Slow walking	
Cooking	
Shopping	
Cleaning up	

Laundry and ironing	
Nursing the children	
Nursing the elderly or disabled persons	
Gardening and cleaning snow	
Home repair work	
Sports	

Nutrition habits

Please answer how often you ate the following foodstuffs last week.

	None	1-2 days	3-5 days	6-7 days
Potatoes				
Rice, pasta				
Porridge, muesli, cereal				
Dairy products				
Fish				
Meat				
Meat products (sausage, frankfurters)				
Fresh vegetables				
Boiled vegetables				
Fresh fruit, berries				
Compotes, jams				
Confectionery				
Non-alcoholic beverages				
Eggs				

- How many cups of coffee and tea do you usually drink a day?
  .....
- How many slices of bread or white bread do you usually eat a day?
  .....

Smoking

- If you smoke, which tobacco products do you use?.....

Number of units a day in the last four weeks	
Number of units a day in the period of highest consumption	

Alcohol

Amount of beer a week in the last four weeks (number of 0,5 l)	
Amount of wine a week in the last four weeks (number of 100 ml glasses)	
Amount of beverages of ~20% vol a week in the last four weeks (number of 4 cl glasses)	
Amount of beverages of ~40% vol a week in the last four weeks (number of 4 cl glasses)	

Questions for women

Time of beginning of menstruation (age in full years)	
Average length of the menstruation cycle	
Time of end of menstruation (age in full years)	
Number of pregnancies	
How did the pregnancies end?	
Time of beginning consumption of hormonal contraceptive preparations	
Time of ending consumption of hormonal contraceptive preparations	
Other hormonal contraceptive	

preparations used	
Time of beginning consumption of other hormonal preparations	
Time of ending consumption of other hormonal preparations	
Hormonal preparations used	

Health condition

There are five short questions about activity, coping with everyday life, pain, and mood.

Diseases and medicaments

Please answer which diseases you suffer from or have suffered from and whether your mother or mother's mother and father or father's father suffered from the same diseases.

Infectious diseases	
Tumoral diseases	
Malignant diseases of blood and lymphoid tissue	
Diseases of blood and haematopoietic organs	
Diseases of endocrinal organs	
Mental diseases, mental and behavioural disorders	
Nervous diseases	
Eye diseases	
Ear diseases	
Diseases of blood circulation organs and heart	
Arterial and vein diseases	
Brain vascular and brain blood supply diseases	
Respiratory and lung diseases	
Dental diseases, diseases of oral cavity and maxillary diseases	
Diseases of bones and joints	

Diseases of urinary and sexual organs	
Disease conditions at the time of pregnancy, delivery, and post-partum	
Congenital diseases and health disorders	

- Which medicaments do you use?
  .....
  .....
  .....
  .....

Measurements

The questionnaire entails measurement of the gene donor's height, blood pressure, heart rate and weight.

Questions and notes

[138] See Lonely Planet's Estonia: History, available online at http://www.lonelyplanet.com/destinations/europe/estonia/history.htm (accessed 24 April 2005).
[139] Lonely Planet, ibid.
[140] Frank, L. Biotechnology in the Baltic. *Nature Biotechnology*, Vol 19. June 2001.
[141] See, for example, Biotechnology in Estonia. Available online at http://www.genomics.ee/index.php?lang=eng&show=17&sub=41 (accessed 22 April 2005)
[142] Lonely Plant, ibid.
[143] *Economist Intelligence Unit* (EIU) Estonia Country Profile, 2005.
[144] Frank, L. Storm Brews Over Gene Bank of Estonian Population. *Science*, Vol 286, Issue 5443,1262-1263, 12 Nov 1999.
[145] Estonia takes on an ambitious project to outline the country's genome. *www.internationalspecialreports.com.* 05 Dec 2001. Available online at http://www.geenivaramu.ee/index.php?show=article&lang=eng&id=131&pid=3&offset=60 (accessed 22 April 2005)
[146] Gross, M. Estonia sells its gene pool. *The Guardian.* 09 Nov 2000.
[147] EIU, ibid.
[148] Meierhenrich, D. Wir sind soooooooo hungrig! *Frankfurter Allgemeine Zeitung.* (Nr. 250, p. 41). 27 Oct 2001.
[149] Estonian Efficiency. *The Lancet*, Vol 364. 23 Oct 2004. More description of the early healthcare systems and its reforms follow verbatim from this article:

Under the Semashko model, named after a Russian doctor, health care was funded from the state budget and directed from Moscow through central planning. A preoccupation with quantitative targets led to overprovision of hospital beds and an unnecessary emphasis on specialist care at the expense of primary services. In Estonia, the number of hospitals was particularly excessive because of the Soviet expectation that the republic might bear the brunt of a military confrontation with the west.

With the regaining of independence (Estonia was a sovereign nation before it was occupied by the USSR during World War II) in 1991, the country embarked on a radical transformation of its health-care system. The two chief tasks were to move from the Soviet model to a decentralized system with the participation of private practitioners, and to change from a state-funded service to one based on health insurance. New legislation introduced in 1992 brought in a nationwide mandatory health-insurance scheme that is paid for by employers through payroll tax, and accounts for two-thirds of health expenditure. Pensioners and young people are also covered and the state pays for groups such as soldiers and jobseekers. A central "sickness fund" contracts all service providers whether public or private, while emergency care is paid direct from the state budget, and in practice covers a wide range of care for the estimated 7% of people who are uninsured.

From the middle of the 1990s another major change was the slackening of state control over hospitals. A long-term plan for the sector was drawn up by Swedish consultants 4 years ago with a completion date of 2015. Scores of the 110 dilapidated Soviet-era hospitals are being converted into nursing homes to prevent bed blocking in acute-care wards.

Mapping studies showed that 19 strategically positioned hospitals should be enough to put no Estonian more than 70 km, or one hour's drive, away. These hospitals will be either municipal or state-owned, but run as limited companies or foundations in an attempt to ensure openness and responsible management.

Meanwhile, something close to a revolution has taken place in primary care. Last year saw the completion of a 6-year programme to retrain employees of Soviet-era polyclinics, turning 807 of them into general practitioners, known as family doctors, who act as independent contractors with the sick fund. It's a far cry from the past when the same employees were pen-pushers with low prestige and low pay who saw their task as referring as many patients as possible to specialists.

The next challenge is nursing care reform: under a package of measures set for introduction by 2007, ambulatory care and coordination with social services will be increased. Evaluation teams are to make more rigorous checks of who needs acute care and who would be better treated in a nursing-care hospital.

As the overhaul of the health-care system continues apace, many hurdles remain. Spending on health is low at 5·1% of GDP, a figure below that in two of the poorest countries in Europe, Moldova and Romania, and it seems unlikely to rise in the near future.

However, [Katrin] Saluvere [deputy director general for health care] says: "We are doing a lot with little money—a small percentage from a small DP—and I think we've built up a very good system. If anybody wants to get some thinking about what efficiency is they should come to us."

[150] Frank, L. Storm Brews Over Gene Bank of Estonian Population, Ibid.
[151] Frank, L. Biotechnology in the Baltic, ibid.
[152] Gross, M. Ibid.
[153] Frank, L. Storm Brews Over Gene Bank of Estonian Population, Ibid.
[154] EIU Iceland Country Profile, 2004.
[155] Frank, L. Give and Take--Estonia's New Model for a National Gene Bank. GNN. 06 Oct 2000. Available online at http://www.geenivaramu.ee/index.php?show=article&lang=eng&id=133&pid=3&offset=80 (accessed 22 April 2005)
[156] Hollon, T. Gene Pool Expeditions: Estonians or subjects of the crown of Tonga: Whose gene pool hides gold? *The Scientist* 15[4]:1, 19 Feb 2001.
[157] Schumer, D. The Genetic Gold Mine. *Frankfurter Allgemeine Zeitung*. 26 Nov 2000.
[158] Two short biographies of Dr. Pikani follow:
Dr Jaanus Pikani is chairman of the Estonian Genome Foundation – a NGO that initiated the Estonian Genome Project, a population based health and genome data collection in Estonia. Responding to the initiative Estonian parliament approved in 2000 special law enabling large scale genomic data collection. Jaanus Pikani has been working more than 10 years as a cancer and reconstructive surgeon. From 1994 he was in different areas of public service (secretary general of the Ministry of Social Affairs, Chief of Staff Estonian President). In 1998 he was appointed as CEO of Tartu University Clinics to conduct a merger of 15 different organisations to the biggest hospital in Estonia. As being among the initiators and architects of the Estonian Genome Project, Jaanus Pikani has followed closely international developments in various aspects of health and genome data collection. Dr Pikani is also a founder of the Estonian biotech company Asper Biotech and serving on the board of the Estonian Biotechnology Association. He is also member of the ScanBalt Steering Committee. [Source: http://www.scanbalt.org/sw812.asp (accessed 25 April 2005)]

Jaanus Pikani (40), Estonian, M.D., Specialist cancer surgeon; Postgraduate education in health economics and management; CEO and Chairman of Executive Board, Tartu University Clinics; Chairman of Supervisory Board of the Estonian Genome Centre Foundation; Director, Office of the President of Estonia (1995-98); Permanent Under Secretary of State, Estonian Ministry of Social Affairs, (1994-95) [Source: http://www.ehfg.org/website00/pikani_tk.html (accessed 25 April 2005)]

[159] Web site: http://www.genomics.ee/
[160] Frank, L. Storm Brews Over Gene Bank of Estonian Population, Ibid.
[161] Estonia takes on an ambitious project to outline the country's genome. www.internationalspecialreports.com. 05 Dec 2001. Available online at http://www.geenivaramu.ee/index.php?show=article&lang=eng&id=131&pid=3&offset=60 (accessed 22 April 2005)
[162]Web site at http://www.geenivaramu.ee/
[163] Breithaupt, H. The future of medicine. *EMBO Reports* vol. 2, no. 6, pp 465-467. 20 Nov 2001.
[164] Frank, L. Give and Take--Estonia's New Model for a National Gene Bank, ibid.
[165] Pioneers in medicine. *EMBO Reports* Vol 4, No 11, 2003.
[166] Hollon, T. Ibid.
[167] Frank, L. Population Genetics: Estonia Prepares for National DNA Database. *Science* Vol 290, Number 5489, p. 31. 6 Oct 2000.
[168] *European Biotechnology Science & Industry News*. Estonian Genome Project: First Blood Samples Received. 10 Dec 2002
[169] Frank, L. Population Genetics: Estonia Prepares for National DNA Database, Ibid.
[170] Habeck, M. Estonia jumps on gene bank train. *The Scientist*, 17 Oct 2002.
[171] Kicking IT Up, Estonian Style. *Bio-IT World*. 10 Feb 2003. Available online at http://www.bio-itworld.com/archive/021003/decoding_sidebar_1944.html (accessed 22 April 2005).
[172] Tasmuth, T. The Estonian Gene Bank Project—an overt business plan. *openDemocracy*, 29 May 2003.
[173] EGeen International Completes $2.0 Million Private Placement. EGeen press release dated 2 April 2002. Available online at http://www.egeen.ee/public/page.php?pid=news_press_2002_04_02_1&mact=news (accessed 24 April 2005). More about the two lead investors, verbatim from the press release:

SEAF is an international venture fund management firm founded in 1989 with headquarters in Washington, D.C. and a worldwide network of funds operating in 14 countries. SEAF manages over USD 140 million, and has made over 190 investments worldwide.

The SEAF CEE Growth Fund LLC ("the Growth Fund") is a USD 16.3 million venture capital fund that invests from $0.5 to $3 million in the best performing, growth-oriented companies in the SEAF portfolio that operate in Central and Eastern Europe. The Growth Fund invested in Asper Biotech, an Estonian genotyping technology company, in 2001 and has made a number of investments in Poland and Croatia. The Growth Fund's investors include the International Finance Corporation (IFC), Deutsche Investitions- und Entwicklungsgesellschaft (DEG), State Secretariat for Economic Affairs Switzerland (SECO), Finnish Fund for Industrial Cooperation (FINNFUND), Pension Fund of the Evagelische Kirche in Hesse und Nassau, Calvert World Values International Equity Fund, and Merifin Capital N.V. The Growth Fund operates from its offices in Washington, D.C. and Warsaw, Poland.

The Baltics Small Equity Fund LLC ("BSEF") is a venture capital fund investing into small and medium sized growth-oriented companies in Baltic countries. BSEF has made 22 investments since 1998, including 12 investments in Estonia. BSEF invested into Asper Biotech in 2000 and was an investor in Regio from 1998 to 2000. The shareholders of BSEF are the European Bank for Reconstruction and Development (EBRD), the Baltic American Enterprise Fund (BalAEF), and SEAF. BSEF operates from its offices in Tallinn, Riga, and Vilnius.

[174] Estonian Genome Project moves forward with funding. *Genome News Network*, 18 Jan 2002.
[175] Hille, S. Das High-Tech-Orakel. *Der Tagesspiegel*. 03 Sept 2002.
[176] EGeen International Completes $4.25 Million in First Venture Financing Round. EGeen press release dated 18 Nov 2002. Available online at http://www.egeen.ee/public/page.php?pid=news_press_2002_11_18_1&mact=news (accessed 25 April 2005). More details on the investors, verbatim from the press release:

About Draper Fisher Jurvetson ePlanet Ventures

Draper Fisher Jurvetson ePlanet Ventures is a global venture capital firm focused on the information technology and life sciences sectors. Draper Fisher Jurvetson ePlanet Ventures was founded in 1999 to take advantage of the growing trend towards globalization in technology by the leading Silicon Valley-based venture capital firm, Draper Fisher Jurvetson (www.dfj.com) in partnership with Europe-based ePlanet partners. Draper Fisher Jurvetson ePlanet Ventures invests in startups throughout the United States, Europe, Israel and Asia. The fund currently operates offices in Silicon Valley (Redwood City, CA), London, Singapore, Beijing, Tel Aviv, Hong Kong and Tokyo.For more information, please visit www.dfj.com.

About Biobank Technology Ventures

Biobank Technology Ventures is a life science venture capital fund focused on creating and developing innovative product-driven biotechnology ventures. Founded in 2001, Biobank invests in projects in California and Europe with a rapid demonstration of proof of concept and the use of a global pool of resources for technology, scientific and managerial expertise, and capital. Besides seed and early stage financing, Biobank provides its network of companies with experienced management support for intellectual property, licensing and business and international development. The fund currently operates with offices in Del Mar, California and Paris, France. For more information, please visit www.biobankcom.com

About Small Enterprise Assistance Funds

SEAF is an international venture fund management firm with headquarters in Washington, D.C. Since its inception in 1989, SEAF has developed a worldwide network of emerging market SME funds operating in 14 countries in Central and Eastern Europe, Latin America, and China. SEAF manages over USD 140 million, and has made over 190 investments worldwide.

[177] Schumer, D. The Balancing rights Genetic Gold Mine. Ibid.
[178] Weber, A. Das Verkaufte Volk. *Süddeutsche Zeitung Magazin*. 23 Nov 2001.
[179] Frank, L. Storm Brews Over Gene Bank of Estonian Population. Ibid.
[180] Tasmuth, T. The Estonian Gene Bank Project—an overt business plan. Ibid.
[181] Rotzer, F. Gendatenbank fur ein ganzes Volk. *Heise*. 15 Dec 2000.
[182] Schrell, A. and Heide, N. in Estonia's gene pool. *Managing Intellectual Property*. London: apr 2001. Iss. 108, p. 52.
[183] Schrell, A. and Heide, N. Ibid.
[184] This section is taken verbatim from the EGPF website, except where otherwise noted. See http://www.geenivaramu.ee/index.php?lang=eng&sub=64&PHPSESSID=13449f11c16e7080b00fd972cff8719f (accessed 25 April 2005)
[185] Schumer, D. The Genetic Gold Mine. Ibid.
[186] Schrell, A. and Heide, N. Ibid.

[187] Frank, L. Storm Brews Over Gene Bank of Estonian Population. Ibid.
[188] Tasmuth, T. The Estonian Gene Bank Project—an overt business plan. Ibid.
[189] Tasmuth. Ibid.
[190] Berg, L. Gen Europa: Estland beginnt mit dem Aufbau der weltgrossten Genomdatenbank. Sie soll die Tur Zur EU offnen. *Berliner Zeitung*. 28 Jan 2002.
[191] Estonia's genome project to be delayed. *The Baltic Times*. 09 August 2001.
[192] Frary, M. Estonian genome project ahead of schedule. *Reuters Health*. 23 Dec 2002
[193] See EGeen press releases at http://www.egeen.ee/public/page.php?pid=news_press&mact=news (accessed 24 April 2005).
[194] EGeen International Pulls Backing from Estonian Genome Project. *Baltic Business Daily*. 23 Jan 2004.
[195] Two Key Figures Leave Board of Estonia's Troubled EGeen. *Baltic Business Daily*. 17 Feb 2004.
[196] Council of Estonia's Genome Project Forces CEO to Resign. *Baltic Business Daily*. 06 April 2004.
[197] Estonia: Genome Foundation Ends Cooperation with Backer EGeen. *BNS Baltic Business News*. 27 Dec 2004.
[198] Estonian Genome Project to Start Firing Employees. *Baltic Business Daily*. 02 Feb 2005.
[199] EGeen Announces Expansion of Clinical Development Capabilities. EGeen Press Release. 08April 2005. Available online at http://www.egeen.ee/public/page.php?pid=news_press_2005_04_08_1&mact=news (accessed 26 April 2005).
[200] Available online at http://www.geenivaramu.ee/mp3/A.Metspalu%20CV.doc.DOC (accessed 25 April 2005)
[201] From EGPF website. See http://www.geenivaramu.ee/index.php?lang=eng&sub=74 and http://www.geenivaramu.ee/index.php?lang=eng&sub=75 (accessed 25 April 2005)

Sweden & UmanGenomics

About Västerbotten and its People

Västerbotten is the second largest county in Sweden and lies in the north of the country. While Västerbotten comprises approximately one-eight of the landmass of the entire country, its sparse population of 255,000 is less than 3% of Sweden's total. About 17% of the population is over 65 years of age, with 19% between 0-15 years old. The largest three cities are Umeå (about 71,000 people), Skellefteå (about 32,000) and Lycksele (under 9,000). Healthcare plays a major role in the economy and employs 8,400 people, especially at the county's three hospitals located in its three largest cities. At 820 beds, the University Hospital of Norrland in Umeå is north Sweden's largest hospital.[202] See Figure 3 for a map of the county.

Archeology has uncovered settlements in Västerbotten around Vuollerim and along the Big and Little Luleå Rivers by hunter-gatherer, perhaps originally from Russia, dating back some 6000 years ago. There also remains a relatively tiny aboriginal population (called Laplanders—only 10,000 remain in all of Sweden).[203] While Västerbotten was involved in some trade and a law (the Lappmarks Proclamation) in 1673 reduced taxes for those willing to move north, the area seems to have remained relatively isolated due to its geography to such an extent that its occupants can still be referred to as a "founder population" [204,205] and as such has a significant role in studies of genes using population genetics.

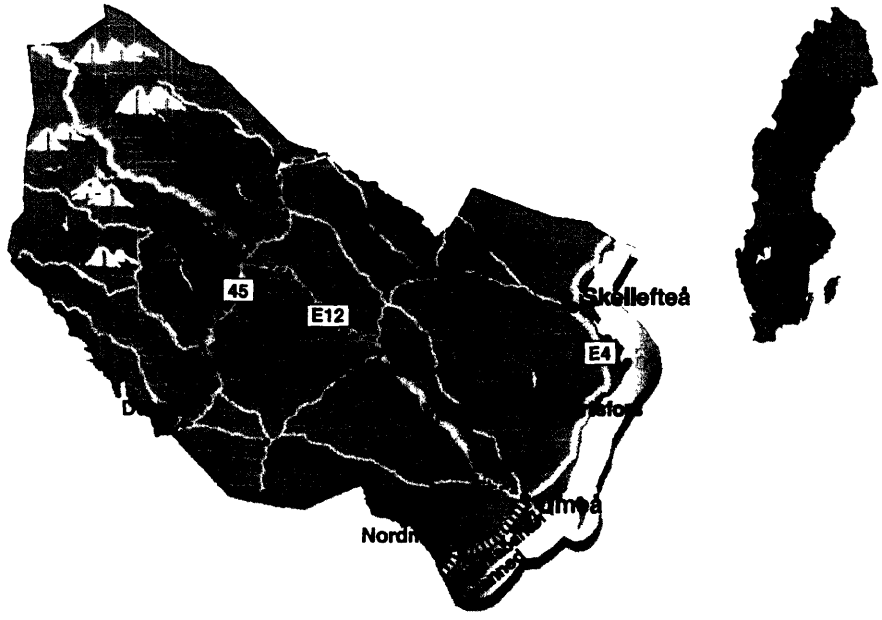

Figure 3: Map of Västerbotten County (left) and Sweden (right), highlighting Västerbotten County. [206]

The Medical Biobank in Umeå

The Biobank consists of three cohorts: Västerbotten Intervention Program (VIP), MONICA and the mammary screening cohorts. These three are also sometimes referred to as Northern Sweden Health and Disease Study Cohort, or simply North Cohort.[207]

MONICA

MONICA (short for "Multinational *MONI*toring of Trends and Determinants in *CA*rdiovascular Disease") is a World Health Organziation (WHO) sponsored study begun in various worldwide centers in the early 1980's to "explain the diverse trends in cardiovascular disease mortality which were observed from the 1970s onwards."[208] There are now 32 MONICA collaborating centers in 21 countries, monitoring 10 million men and women aged 25-64. According to the MONICA website, the project has set standard and quality control methods for data collection. These methodologies include:[209]

- standardized coronary and stroke event registration, including collection of data on diagnostic information.
- data on medical care of patients before, during and after the attack. The methods have been developed taking into account the local characteristics of the health care system in each Centre.
- risk factor measurements through sample surveys of the study population. This includes
    - identification of suitable sampling frames.
    - sample selection.
    - methods for obtaining optimal response rates.
    - standardized valid measurement of the main cardiovascular risk factors, with focus on
        - smoking habits
        - blood pressure and its treatment
        - serum or plasma total and HDL cholesterol
        - height, weight, marital status and education
        - Also, methods have been developed to collect data on a number of aspects of more recent interest, like awareness and treatment of high cholesterol, use of aspirin and contraceptive pills, and on menopause.
- routinely available data on population size and mortality in the study populations.
- medical services data through
    1. a special inventory of services, diagnostic and therapeutic procedures for the management of coronary heart disease available to the populations of Centres, 1980-1994.
    2. routinely available data on hospital admissions for management of coronary heart disease (including coronary artery procedures).

Regarding structure and funding:

> The WHO MONICA Project is a partnership between the World Health Organization and the MONICA Principal Investigators. Between the infrequent meetings of the MONICA parliament - the Council of Principal Investigators - the running of the project is carried on by designated MONICA Centres...The World Health Organization acts as project sponsor and co-ordinator, assists in acquiring funds, and executes financial and other contracts whenever necessary. The

> general management and coordination of the WHO MONICA Project are carried out from WHO Headquarters [in Geneva] by the Cardiovascular Diseases Programme within the Division of Noncommunicable Diseases, the MONICA Management Centre. Responsibility for the management of the major technical aspects has been assigned to different centres with expertise in the specific fields.[210]

Sweden has two MONICA centers, one in Gothenburg (south), and the other encompassing the two northernmost counties in Sweden, Västerbotten and Norrbotten, which is roughly the same area as England and Wales combined.[211] Both counties are sparsely populated (combined: about 510,000 people), split roughly 50/50 between urban and rural dwellers. Socioeconomic status is low and mortality and unemployment are above average. Sweden North is the northernmost cohort of all in the MONICA study. This may have played a role in the inclusion of this region in MONICA because "[p]revious epidemiological data suggest that there is a general tendency towards higher [cardiovascular disease] mortality in countries on higher latitudes, at least within Europe."[212]

Two principle investigators were listed for the Northern Sweden group: T. Messner are the Kalix Lasarett Department of internal medicine and K. Asplund at Umeå University Hospital Department of Medicine[213] MONICA Sweden North invited 2,000 people between the ages of 25 and 64 each year in population-based surveys in 1986, 1990 and 1994; there was follow-up in 1999. The response rate was 81.3% (1625 participants out of 2000 invited) in 1986.[214] At the conclusion of the study there were a total of 7,500 unique individuals and 11,500 sampling occasions.

Västerbotten Intervention Program (VIP)

VIP, a collaboration between Västerbotten city council and researchers at Umeå University started in 1985, was designed to conform to the MONICA standards outlined above and was conceived as "a community intervention programme on [cardiovascular disease] and diabetes prevention".[215,216] Methods of intervention were on the individual counseling level (advice on diet, exercise and smoking) and also the community level:

> For example, at the beginning of 1987 a food labeling system was introduced in the shops in Norsjö [See Figure 3], where foods with a low-fat and/or high fibre content were marked with a special heart symbol. The use of unconventional health education activities and methods such as drama, music and informal meetings has been encouraged.[217]

Women and men from the entire Västerbotten area were invited to participate when they turned 30, 40, 50 and 60 year old. It was estimated that 40,000 people had entered VIP by the end of August 1996[218], growing to 74,000 people (67,000 had given blood samples) by 2002. Like MONICA, primary care physicians would give participants a health survey. A blood sample was also requested after having fasted for at least four hours. It was stored at the Northern Sweden Medical Research Bank (NSMRB).

While it is not entirely clear what funding mechanisms were used to fund the study, it is clear that "[c]onstitutionally, the counties are local government units with taxing powers, charged with the responsibility of providing healthcare to the citizens in their jurisdiction within a legal framework that gives them almost total freedom from central governance to formulate their own healthcare policies."[219] In 2000, about 86% of the county's operating budget was spent on healthcare, allocated ultimately by the County Council and delegated to the County Executive Board. It is assumed that VIP was funded through this public mechanism, though it is unclear which bodies and individuals are significant players.

The majority of BioBank samples come from VIP. VIP was terminated for political reasons in 1997 according to one source[220], though the UmanGenomics web site states that the cohort "is increasing with 5,000-6,000 new samples annually."[221]

Mammary Screening

Mammary screening began in 1997 with routine every-other year sampling of individuals between the ages of 50 and 69. There were 25,700 unique individuals for a total of 44,000 sampling occasions.

Biobank

Göran Hallmans of the Department of Public Health and Clinical Medicine/Nutritional Research, University of Umeå is the highest-ranking scientist of Biobank, which is considered "population-based" (or nearly population based—that is, covering much of the population in a statistically representative way). The entire Biobank cohort currently contains about 85,000 individuals and 130,000 tissue samples. For details of Biobank contents, see footnote.[222]

A number of significant publications have come from Biobank-related studies. In addition to about 15 publications that reference VIP on PubMed,[223] the Medical Biobank website[224] references the following five papers:

- Kaaks, R., et al. Prospective study of IGF-I,IGF-binding proteins, and breast cancer risk, in northern and southern Sweden. Cancer Causes Control. 2002 May;13(4):307-16.
- Bingham, S.A., et al. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. Lancet 2003, May;361:1496-1501.
- Mork, J., et al. A prospective study of human papillomavirus infection as a risk factor for head and neck carcinomas. New England Journal of Medicine. 2001, 344:1125-1131.
- Stattin, P., et al. Plasma IGF-I, IGFBPs, and prostate cancer risk; a prospective study. 2001, JNCI 92: 1910-1917.

- Wallin, K.L., et al. Type-specific persistence of human papillomavirus DNA before the development of invasive cervical cancer. 1999, The New England Journal of Medicine 341:1163-1168.

While cardiovascular diseases and diabetes certainly show up on the list of publications, so do "life style" studies, various viral infections, cancer, and a number of other areas. In other words, the Biobank seems to be useful for a wide variety of studies.

Early (Public) Relationship Between Biobank and Cohort Members

As noted above, Biobank was established by the University and City Council. There was therefore clear government-level approval for this effort. Also, healthcare played a strong role in the economy and identity of this county; perhaps the culture of healthcare led to a high degree of participation by residents. On the individual level, one source notes that "[s]ince the beginning, each individual has been asked to sign a donation form, which says that the sample is donated for "future disease-preventing research".[225] While few other details of the early relationship of cohort members with Biobank, this wording was important because it enabled the later commercialization of the Biobank.

The Advent of UmanGenomics and Shift from Public to Private

The idea of commercializing the Biobank began in the mid-1990s, initially conceived of as a joint venture with a large company like AP Biotech.[226] As an alternative to a JV,

> ...together with [Hallmans, biobank chief scientist's] colleague Joakim Dillner, [Hallmans] proposed a social-enterprise model in which ownership would be vested in a foundation representing the people of Västerbotten. This was to be managed by the researchers, the county and the university, as well as by potential funders such as the Knut and Alice Wallenberg Foundation. All profits were to be reinvested into biobank research. Hallmans' group saw this as meeting the trust placed in them by the donors, benefiting research and honouring the bank's commitments to its existing funders. But the plans drawn up by the university and the county cut across this scheme.[227]

The "scheme" referred to is that for UmanGenomics (the word Uman is a play on Umeå). "UmanGenomics grew out of the shared wish of the university and Västerbotten's county council to commercialize the biobank that had been created under their auspices. The original plan was to 'discover disease-related genes, explore their function and market this knowledge.'"[228]

UmanGenomics was established in 1999 with an exclusive commercial license on Umeå's Medical Biobank.[229] The deal was structured in such a way that the university and health department had a 51% share in the company.[230]

Nature of Commercial Relationship

While the involvement of the local government and university facilitated full transfer of the Biobank assets (and associated consents) to UmanGenomics, the Swedish Medical Research Council (MRC) swiftly implemented "Europe's fullest set of ethical guidelines on the use and control of 'biobanks'"[231] soon after UmanGenomics was founded. The MRC guidelines include:

- Anonymization of samples and records with codes; the code key is kept in a public institution.
- An independent ethics committee to control all access to the bank. The ethics committee also has layperson representatives and politicians involved.[232]
- Seeking informed consent from donors when their sample is used for a new purpose
- Proper storage and safeguarding of the bank

UmanGenomics was cited as "a model of how public tissue banks should interact with the biotech industry".[233]

New Swedish laws were introduced in 2003, and a new contract was negotiated and signed among the university, local government and UmanGenomics.

> The Swedish Government's Bill 2001/02:44 on Biobanks in Health Service etc., was passed by the Swedish parliament, the Riksdag, on May 16, 2002.
>
> Art. 3. If a biobank is to be used in purposes regarding research or clinical trials then decisions according to Art. 1 can only be made after examination and authorization by a bioethics committee. The biobank can in such cases not be used for other purposes than those previously decided upon, without the committee's authorization.[234]

Furthermore, a draft version of the contract dated April 22, 2002, stated payment terms:

> Uman shall make payments of the set amount of two (2) million Swedish kronor [USD 195,000 at 2002 exchange rate;[235] USD 283,000 at 2005 exchange rate[236]] per year for part of the cost of running the Medical Biobank. If this cost changes, the amount shall be subject to renegotiation. The aim of the renegotiation shall be to find a level at which to set the amount which is reasonable with consideration to the cost of running the Biobank[237]

Result

UmanGenomics appears to have all but failed, but because of IP issues, not access to data:

> Unlike many countries, Swedish law allows for 'the teacher's exception', which gives academics ownership of the intellectual property that they produce. But legally it remains unclear how this exception relates to biobanks. The contract drawn up to allow UmanGenomics access to the Västerbotten biobank recognizes only the county and the university as "principals with rights of disposal" over the data the bank holds. Hallmans, as the chief architect behind the biobank's creation, is challenging this interpretation.[238]

Hallmans objects to a number of aspects of Uman contract. Specifically, he does not like the exclusivity of the commercial contract; that donors did not know or consent to selling their samples to a for-profit company; and that his intellectual property considerations were not taken into account.
[The last report I can find has his case in appeals court...I can't find any English language reporting of the outcome of this court case!! Or any other news about the company after this piece, for that matter!]

The corporate website for UmanGenomics[239] does make it look like a company that had been mothballed. It shows three press releases:

2003-09-01 Balticgruppen and new CEO
Balticgruppen becomes part-owner of UmanGenomics AB. Anders Blom enters the position of CEO.The mission will be to restructure the business idea to meet the markets demands.

2004-12-09 Cooperation Agreement
UmanGenomics has recently signed a cooperation agreement with professor Dan Holmberg, head of the unit for medical- and clinical genetics at the University of Umeå. The object is to analyse both family-based gene material and prospective material from the Umeå Biobank in order to identify genes assocated to diseases..

2005-02-02 Collaboration on variant form of NGF beta
UmanGenomics has signed an agreement with a research group that has discovered a mutant form of the nerv growth factor beta gene that is associated with loss of pain perception. This NGF mutant may have applications in the treatment of Alzheimer's disease. The agreement allows UmanGenomics to commercialise the scientists findings.

It seems to show very little activity and presumably academic-only collaborations.

The *Nature* article seems to have the final word: "As Umeå—company, county and university—has sadly learnt, failing to keep all the stake-holders on board is expensive."

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[202] County Administration of Västerbotten and Västerbotten City Council. "Facts about Västerbotten 2003". June 2003. Available online at http://www.vasterbotten.se/faktaomlanet/AC_eng_03.pdf (accessed 14 April 2005).
[203] The History of Lappland, Norrbotten and Västerbotten, available online at http://www.sverigeturism.se/smorgasbord/smorgasbord/provincial/lappland/history/ (accessed 14 April 2005).
[204] See http://www.jax.org/courses/archives/2004/hlb04_austin_presentation_2.pdf (accessed 14 April 2005).
[205] "The *founder effect* occurs when populations are started from a small number of pioneer individuals of an original population. Due to small sample size, the new population could have a much different genetic ratio than the original one. An extreme example would be that which results when a plant population is established by a single seed." A "founder population" is therefore the resulting population from such a founder effect event. From http://tidepool.st.usm.edu/crswr/founder.html, accessed 18 April 2005.
[206] Ibid, County Administration of Västerbotten and Västerbotten City Council.
[207] Medical Biobank, http://www.biobanks.se/medicalbiobank.htm (accessed 14 April 2005).
[208] See http://www.ktl.fi/monica/ accessed 18 April 2005.
[209] Verbatim from http://www.ktl.fi/monica/public/datacomp.html accessed 18 April 2005.

[210] From MONICA Manual, http://www.ktl.fi/publications/monica/manual/part1/i-2.htm accessed 18 April 2005.
[211] Huhtasaari F, et al. Cardiovascular risk factors in the Northern Sweden MONICA Study. Acta Med Scand. 1988;224(2):99-108.
[212] Ibid.
[213] http://www.ktl.fi/monica/public/popu/nsweden.html accessed 18 April 2005.
[214] Huhtasaari ibid.
[215] Laage-Hellman, Jens. The industrial use of biobanks in Sweden: an overview, which is a shortened English version of a longer Swedish report: Laage-Hellman, J., *Kommersialisering av svenska biobanker: ett näringspolitiskt perspektiv* IMIT-report, Institute for Management of Innovation and Technology, 2001, forthcoming. Available online at http://www.bioethics.uu.se/projects/biobanks.html (accessed 13 April 2005).
[216] Weinehall, L et al. Perceived health modifies the effect of biomedical risk factors in the prediction of acute myocardial infarction. An incident case-control study from northern Sweden. *Journal of Internal Medicine* 1998; 243:99-107
[217] Brännströmm I, et al. Changing Social Patterns of Risk Factors for Cardiovascular Disease in a Swedish Community Intervention Programme. *International Journal of Epidemiology* Vol 22, No. 5. 1026-37.
[218] Ahmed E, et al. Anticardiolipin antibodies are not an independent risk factor for stroke: an incident case-referent study nested within the MONICA and Vasterbotten cohort project. Stroke. 2000 Jun;31(6):1289-93.

[219] Kaati, et al. The Quality and Use of Knowledge in Health Policy-Making: A Case Study. *Critical Public Health*, Vol 14, No 3, 225-237, September 2004.
[220] Ibid.
[221] See http://www.umangenomics.com/default.asp?ML=3796 (accessed 19 April 2005).
[222] Biobank content, verbatim from Medical Biobank, Ibid:
Life-Style Questionnaire: Every attending subject is asked to answer a questionnaire, which in the VIP and MONICA-projects includes questions about education, occupation/working conditions, daily habits including smoking, diet etc and in the mammary screening cohort on reproductive conditions. The dietary questionnaire has been validated twice. The data from the questionnaires, as well as from results from the biobank, are kept in a database for future research purposes. The questionnaires in the VIP and the MONICA project are optically read. Measurements: Blood Pressure, Anthropometry, Glucose Tolerance Test, Blood Lipids

Blood Samples: The attendants are asked for their willingness to donate a sample of 20-ml whole blood for future analyses. The sample is taken after 4 hours of fasting or in the morning after an over night fasting (most samples) in the VIP and MONICA cohorts. The 20-ml sample is divided into 10 subsamples consisting of 6 plasma, 2 leukocyte (buffy coat) and 2 erythrocyte samples. All material is frozen at -80° C. The organisation of the bank is elaborated with specially trained staff and an organisation of transport-, storage- and security facilities. For DNA handling a specialised laboratory has been built up.

End-points: Mortality, Cancer events, Cardiovascular events, Other morbidity, Other registry-based follow-up Registries: At regular intervals the cohort is scanned for incident myocardial infarctions (MI) and stroke utilising the Northern Sweden MONICA registry and for cancer using the regional cancer registry. In the future the same procedure will be applied also on other registries e.g. diabetes, osteoporosis, dementia.

[223] Ahmed E, et al. Anticardiolipin antibodies are not an independent risk factor for stroke: an incident case-referent study nested within the MONICA and Vasterbotten cohort project. Stroke. 2000 Jun;31(6):1289-93.

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[224] Medical Biobank, Ibid.
[225] Laage-Hellman, J. Ibid.
[226] Ibid.
[227] Rosa, H. An Ethical Dilemma. *Nature* 425, 123 - 124 (11 September 2003).
[228] Ibid.
[229] Laage-Hellman, J. Ibid.
[230] Sweden sets ethical standards for use of genetic 'biobanks'. *Nature* 400, 3 (1 July 1999).
[231] Ibid.
[232] Racine, E. Discourse ethics as an ethics of responsibility: comparison and evaluation of citizen involvement in population genomics. *Journal of Law, Medicine & Ethics* 390, 31;3. (22 Sept 2003)

[233] Nilsson, A. & Rose, J. *Science* 286, 894 (1999)
[234] See http://www.mannvernd.is/english/news/UG_overview.html (accessed 14 April 2005)

[235] 10.27 SEK/USD, listed at http://www.triacom.com/archive/exchange.en.html (accessed 19 April 2005).
[236] 7.0721 SEK/USD as per *Wall Street Journal* 19 April 2005.
[237] Research and Cooperation Contract (English Translation). Available online at http://www.mannvernd.is/english/articles/UG_research_co-op.doc (accessed 14 April 2005)
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Iceland/deCODE

History and Population of Iceland

The first humans to dwell in Iceland were Irish monks, "who regarded the island as a sort of hermitage until the early 9th century."[240] The Age of Settlement occurred between 870 and 930, when many permanently left a politically turbulent Scandinavia to settle on Iceland.

> Iceland then became a launching pad for explorations of the North Atlantic: Eric the Red, who grew up in Iceland as the son of a Norwegian exile, colonised Greenland in 982, and Eric's Icelandic son, Leif Eriksson, is popularly held to be the first European to explore the coast of North America—which he named Vinland the Good. One of the more reliable Icelandic sagas, however, suggests that Leif Eriksson learned of Vinland from another Icelander, Bjarni Herjolfsson, who had sighted it some 14 years earlier. Whatever the truth is, these voyages of exploration became the source material of one of Europe's great literary flowerings [lyric poetry, followed by epics in the 1100s and 1200s].[241]

However, by the early 1200s, Iceland had entered a violent time known as the Sturlung Age. In the midst of the chaos, King Hákon Hákonarson of Norway imposed himself, making Iceland a Norwegian possession that was exploited and plundered. Widespread death occurred in the 14th century with the eruption of Mt. Hekla in 1300, 1341 and 1389 and epidemics of the Black Death beginning in 1349, "effectively cutting off trade and supplies."[242]

The 14th century closed with the Danes taking control. "Throughout the next two centuries, Iceland was crippled by rampant Danish profiteering, beset by international pirates and subject to an increasing number of natural disasters."[243] However:

> Denmark's grip on Iceland was broken in 1874 when Iceland drafted a constitution and was permitted to handle its own domestic matters. Iceland was released from Danish rule in 1918, making it an independent state within the Kingdom of Denmark, with Copenhagen retaining responsibility for defence and foreign affairs. However, in 1940, Denmark was occupied by Germany. Iceland realised that the Kingdom was in no position to continue overseeing its affairs and, a year later requested independence. It was granted on 17 June 1944.[244]

The country has remained independent since. It still relied on an economy of fishing and whaling, industries that had both suffered heavy losses and conflict with other countries over rules and quotas. The country's population today stands at approximately 280,000 people. It is said that between 625,000[245] and 750,000[246] people total have ever lived on Iceland.

It had been purported by many (recently, especially by those supporting the deCODE project) that the country's populace constituted a homogenous founder population. "Iceland's 280,000 inhabitants descended from a common set of ancestors (Norse and Celts) who arrived there in the ninth century. Because the country's population was virtually isolated until World War II, it has remained remarkably homogeneous and thus provides population genomics researchers like [deCODE founder Kari] Stefansson with an ideal resource." Speculations of the Icelandic population's "purity" were backed up with deCODE-funded scientific studies:

> According to deCODE's research an analysis of Icelandic genealogies that were traced back to two cohorts of ancestors in the 18th and 19th century reveals that the "vast majority of potential ancestors contributed one or no descendants, and a minority of ancestors contributed large numbers of descendants" (Helgason et al. 2003:1370). The "frequencies of a number of mtDNA lineages in the Icelanders" are also said to "deviate noticeably from those in neighboring populations, suggesting that founder effects and genetic drift may have had a considerable influence on the Icelandic gene pool" (Helgason et al. 2000). The findings reveal a high frequency of certain genomic variants because they are descended from a small group of founders. The Icelandic genome is therefore said to be determined by a "founder effect", and that is supposedly very advantageous for deCODE's research because genetic variation can be traced to a "single ancestor in the distant past" (*New York Times*, September 22, 2003). DeCODE's annual report from 2000 stresses precisely this idea adorned with a picture of the statue of the first settler of Iceland, Ingólfur Arnarson who arrived in 874, and in front of the statue a modern day young blonde with apparently bleached hair and a glossy lipstick.[247]

However, this concept of Icelanders as a pure founder population has been challenged, most notably by a population geneticist at the University of Iceland known Einar Árnason.[248] In a published response to a *New York Times* article by Sarah Lyall about deCODE's research in Iceland, Árnason was quoted as writing that:

> deCODE genetics has evoked the myth of the homogenous Aryan Icelanders to entice foreign investors. And in Iceland the company has rallied support for its plans by inventing genetic nationalism, declaring that the Icelandic DNA is superior to all other DNA. Apparently, Ms. Lyall is also a believer, stating "that there has been little immigration to muddy the genetic pool over the centuries". The implication is that immigrants muddy or dirty the genetic purity of the population. By the same token, how would the author characterize the population of New York City?[249]

It seems that Helgason, the lead author on deCODE's paper talking about genetic homogeneity, and Árnason, who decided Icelanders are modestly heterogeneous, drew their different conclusions from quite similar data and results:

> When the findings of Helgason et al. and Árnason are compared, the differences are not that great. When the mean number of paired differences of mtDNA [mitochondrial DNA] is measured, both Helgason et al. and Árnason come to similar results in terms of the ranking of Icelanders on the scale of European populations. According to deCODE's findings, Icelanders rank number eight on a list of 25 populations. According to Árnason, they are the ninth on the list of 26 populations. When considering statistics based on the number of haplotypes, the differences are greater with Icelanders ranking 17 out of 25 populations (Helgason et al.), or they rank 13 out

> of 26 populations (Árnason).) On the basis of these results we get opposing interpretations. Helgason et al. claim that Icelanders are relatively homogenous, and Árnason says that they are an average, heterogeneous European population.[250]

On first glance, this controversy over purity may seem academic. However, implicit in deCODE's business plan was the assumption that a genetically pure gene pool was more important for elucidating genes than would be a heterogeneous one. Of course, other projects like those in Estonia and the UK have used the opposite argument—that heterogeneity of the gene pool is important so that a project's results may be applicable to a broader pan-European population. The scientific fact seem to be less important, though, than deCODE's initial marketing and rhetoric that frequently referenced purported homogeneity to sell the project to both investors and the Icelandic people. DeCODE's claims of purity were therefore criticized when "evidence" to the contrary came to light, in an attempt by opponents to attack the deCODE project itself and ultimately, it is presumed, sway public opinion.

Genealogy, Healthcare and Prior Studies

Icelanders are said to have a passion for genealogy:

> The origins of this passion, explains Arni Bjornsson, an ethnologist at the National Museum of Iceland (and formerly [deCODE founder] Kari's high school Icelandic teacher), go back to the settlers. Most of them were not so much Viking raiders as poor peasants escaping an oppressive Norwegian king. When they landed in empty Iceland, they acquired farms the size of Liechtenstein. It became important to know clearly who stood to inherit such homesteads-and the Icelandic convention of adopting patronymics rather than family names offered little help. People in Iceland were then and still are known by their first names. Thus Kari is Kari to everybody, whether they've met him or not. The surname Stefansson just signifies that he is the son (and not the daughter) of Stefan. In such a system, the easiest way to know your family relations is to record them scrupulously generation by generation.
>
> This the Icelanders have always done. The sagas are thick with family trees, and genealogy is a popular hobby today; one of the newspapers publishes a weekly column on the subject. And when an Icelander dies, the obituary begins with a full list of parents and progeny, including their dates of birth and death.[251]

This passion is also aided by sources like detailed church records and censuses dating to the 18th century.[252] Such records allow Icelanders to trace "...family ties to 75 percent of all the Icelanders who have ever lived."[253]

Healthcare records are also plentiful and detailed. Iceland's universal healthcare was established in 1915 when the National Health Service was formed. Detailed records have been kept since then and are accessible because "[i]n the Icelandic system, people with specific diseases are funneled into specialized treatment centers, which makes them easy to find."[254] Tissue sample collection began in the 1940's.[255]

The Icelanders have engaged in prior nation-wide population research for a variety of diseases. For example, a study published in 1990 looked at systemic lupus erthematosus cases in all of Iceland for the ten year period from 1975 through 1984.[256] A population study on BRCA2/breast cancer was published in 1998.[257] This study talks about the Icelandic Cancer Registry (ICR), stating that it "contains information on all cancer cases in Iceland since 1955 and all breast cancers since 1990. All data on cancer are based on medical records, and include 947 breast-cancer pedigrees." There are numerous other examples of Icelandic population studies in the scientific literature.

DeCODE and the Act on Health Sector Databases

DeCODE was founded by Iceland native Kari Stefansson. Keri received his M.D. at Iceland's only university, in Reykjavik, and then went to the University of Chicago to specialize in neurology and neuropathology. In 1993, fifteen years later and after having earned tenure at Chicago, he moved to Harvard and Boston's Beth Israel Deaconess Hospital where he became head of neuropathology.[258] After spending time there,

> ...Stefansson had grown frustrated with the pace of academic research. At the time, he was studying multiple sclerosis and had become convinced there were inherited factors involved. And he was beginning to see the disease and its genetic roots as an information technology issue....Even before DeCode was given the go-ahead to create the national medical records database, it had begun to work on the genetics of specific diseases, using the enormous amount of data available on the local population along with blood samples from willing participants.[259]

Decode was founded in 1996[260] as a U.S. company headquartered in Delaware with a substantial subsidiary in Iceland. It describes itself as "...a genomics and health informatics company which is developing products and services for the healthcare industry. We use our comprehensive population data and proprietary data-mining tools to identify and analyze the genetic factors involved in common diseases...[bringing together] three key types of anonymized data on the Icelandic population: public-domain genealogical data, and genotypic and clinical data gathered from volunteer participants in our gene research programs."[261] According to founder and native Icelander Kari Stefansson, incorporation in the United States was important to secure funding, "[b]ut Kari persuaded his financiers that deCODE would never fly, from a public relations point of view, if it was perceived as American. It would too easily be seen as an exploitation of the Icelanders—as indeed other genetics companies have been accused of exploiting other isolated populations, such as the Easter Islanders, by flying in and taking their blood and leaving little behind."[262]

Thus, Kari and deCODE were the driving force behind the Icelandic Healthcare Database. Given this goal, the company raised venture capital followed by a $244 million IPO in July 2000.[263] DeCODE also

entered into a number of collaborations: early on, the company established a five year nonexclusive[264] $200 million contract with Hoffman-La Roche[265] and collaborated with Partners HealthCare of Boston.[266] Later, they were reported to also be working with Merck[267] and IBM[268].

Health Sector Database Act

Kari was reported to have had the database in mind for some time, "[b]ut to make it happen he need[ed] a law authorizing its creation and especially giving deCODE some sort of exclusive commercial right to it. When such a bill was introduced in the Althing, the Icelandic parliament, on March 31 [1998], the storm broke."[269] The first draft was said to be "badly written", mainly by deCODE.[270]

The law, officially known as the Act on a Health Sector Database no. 139/1998, "[made] it legal for a private company to construct an electronic database of the country's health records. deCODE...received an exclusive license to build a database of Iceland's medical records (including diagnoses and test results, treatments and side effects) and will be able to combine and analyse these with genetic and genealogical data. The act also grants deCODE exclusive rights to commercial exploitation of the database for 12 years."[271] The bill was debated publicly for about nine months. A poll just before the parliament vote showed that 75% of the Icelandic population supported the bill while 25% opposed it.[272] The bill passed into law in December 1998 by a vote of 37 to 20 with two defections from the ruling coalition.[273] It went into effect in January 2000.[274]

The deCODE-Iceland Relationship

The Health Sector Database act authorized the Icelandic Ministry of Health to issue an exclusive commercial license to "create and manage an electronic database of the country's medical records."[275] This license was granted to deCODE for a period of 12 years, beginning in January 2000. It was anticipated that it would take five years from start to get the database up and running; and the database "will be subject to a review in 2008, and at that time, in accordance with an agreement [deCODE] entered into with the Ministry [of Health] simultaneously with the granting of the Icelandic Health Sector Database license, [deCODE] and the Ministry will enter into discussions on renewal of the license at the end of the term. The Ministry might not renew the Icelandic Health Sector Database license..."[276] Furthermore, "[a]t the expiration of the Icelandic Health Sector Database license, [deCODE is] required to ensure that the Ministry or its designee will receive, without payment of consideration, intellectual property rights necessary for the creation and operation of the database for public health purposes and for scientific research."[277]

The database will consist of both genotype and phenotype information. Phenotype will be assembled through genealogical and healthcare records automatically.

> Iceland's Health Sector Database has been controversial in part because its authorizing legislation does not require that Icelanders give their informed consent before their clinical medical records [and genealogies] are included in the database. Instead, the legislation gives living Icelanders a chance to opt out. They can file a form with the government stating that they do not wish to participate in the database...There is no requirement that Icelanders be told of the specific research uses of their data.[278]

In the past, it was suggested that this "[f]orm will prevent the addition of any new data on [those opting out of] the database, although it will not lead to the removal of any data that has already been entered."[279] However, after protracted disputes with the Icelandic Medical Association (IMA) and others, a summer 2001 press release jointly released by the IMA and deCODE backpedaled on this:

> If information on a patient's health, contained in medical records and stored in healthcare institutions or by independent physicians, has been transferred to a Health Sector Database according to the legislation on such a Health Sector Database and the patient wishes that this information be deleted from the database, it shall be done immediately after the wish has been put forth.
> The operator of a Health Sector Database shall develop methods to delete information from the database and pledges not to commence the transfer of health information into the database until they have been fully developed.
> A demand for the deletion of a patient's health information from the Health Sector Database shall be addressed to the Medical Director, who shall see to it that the demand is implemented. deCODE genetics will pay the costs incurred in processing and executing such demands.[280]

Records of any baby born in the public healthcare system will be included unless parents explicitly opt them out.[281] The deceased were also to be included[282] (though see "Results" below for a recent court case that may have changed this). Stefansson defends "presumed consent"—that is, having to opt out--from widespread criticism emanating from groups domestic and international, including doctors and an organization called Mannvernd[283]:

> Health-care information is going to be collected with presumed consent...and there's not a single place in the world where people use information produced in the process of delivering health care with anything except presumed consent. There is not a single significant study in your country where people have demanded informed consent for the use of information produced in the process of delivering health care...you should link about the consequences of demanding informed consent for secondary use of health-care information...because you would not be able to do epidemiology as we do it today. If it had been required in the past, we wouldn't have the health-care system that we have today... [284]

Genotypic data (DNA obtained through blood samples), on the other hand, are acquired only by donation with informed consent. "We have to get informed consent from people to give their blood, to isolate the DNA, to genotype and then cross-reference that with healthcare information,"[285] says Stefansson. Another source states that "[p]articipants who provide blood for DNA analysis are to give noncompelled

consent, and fair compensation has been negotiated for research subjects [though it is not apparent how individuals are actually compensated] and the nation. These and other issues (some of them rights in the context of the Nuremberg Code) are regulated by national legislation and time-limited contracts."[286] Information and samples were to be collected through deCODE's "agreements with Icelandic health institutions and self-employed health service workers."[287] The data is then encrypted:

> Until March 2001, the medical data, blood samples and genealogical information DeCode has access to was sent first to the Icelandic government's Data Protection Commission, where the personal identification numbers on them were encrypted and then sent on to DeCode. One or two government workers did the encryption, an iffy system that created some lag time. "It's a definite security risk if a government worker has an encryption key in his wallet that he might lose," [Hakon] Gudbjartsson [head of deCODE software development] says.
> To address such risks, DeCode developed an encryption tool known as the Identity Protection System. After months of testing the system, the government replaced those individuals carrying encryption keys in their pockets with the automated encryption software. The encryption takes place at the Noatun Research Services Center, a blood collection facility financed by DeCode, where doctors send those patients who agree to participate in DeCode studies. The Data Protection Commission of Iceland members can log in remotely and find out what data has been sent back and forth and halt the process if they so choose.[288]

There were still concerns, about this scheme, though, because a small population size makes it "...easy to figure out individual identities based on clinical data, even if personal identification numbers are encrypted."[289] While Mannvernd filed law suits because of this privacy issue, it is unclear what became of them or whether the encoding system was further modified.

There were also a number of government oversight committees: "The Monitoring Committee, the Data Protection Commission of Iceland and an Interdisciplinary Ethics Committee will supervise [deCODE's] construction and operation of the Icelandic Health Sector Database. These committees report to the Ministry [of Health]. In addition, the Icelandic Bioethics Committee will review [deCODE's] operation of the Icelandic Health Sector Database." The Ministry of Health, therefore, retained the ability to revoke the license for any number of violations.[290]

What does Iceland—government and citizens—get in return?

As mentioned above, deCODE will build IT infrastructure within the healthcare system using private money—perhaps $100 million or more--and may have to turn it over to the Ministry of Health at the conclusion of the license. In addition to the benefits of building healthcare IT and creating jobs in the alluring new field of biotech, the government would have full access to the database.[291] After criticism, deCODE agreed to share profits with the government, not to exceed approx. $1 million per year.[292] DeCODE also indemnified the Icelandic government "against all damages and costs in connection with...litigation" related to the Icelandic Health Sector Database.[293] Also, deCODE's agreement with

Roche "...gives all Icelanders free access to those drugs and tests" developed based on genes discovered by deCODE.[294]

Results

Opposition group Mannvernd announced on 30 March 2004 in a dramatic headline "The Icelandic Health Sector Database Act stricken down as unconstitutional. A Landmark Decision by the Icelandic Supreme Court."[295] The organization reported on the case of Ragnhildur Gudmundsdottir versus the State of Iceland, in which "Ms. Gudmundsdottir objected to the transfer of data belonging to her deceased father to the HSD [Health Sector Database]. The Icelandic Supreme Court sided with Ms. Gudmundsdottir and struck down the HSD." Interestingly, no mention of this "striking down" can be found in deCODE's press releases or even in analyst reports issued around that time. It seems to have been a non-issue for the company.

Indeed, despite early concerns and criticism, deCODE and the database seem to be doing quite well. It was reported in September 2004 that 110,000 Icelanders had donated DNA to deCODE.[296] A later poll showed that "popular support had risen to 91 percent"[297] and anecdotally, it was stated that "almost everyone [a certain reporter] met in Iceland, from cab drivers to patients, now embraces the effort."[298]

After the initial 1998 $200 million five-year collaboration with Roche, a new $300 million partnership was announced with Roche Diagnostics in 2001, followed by a $90 million deal (exclusive of royalties) with Merck to study obesity.[299] DeCODE also boasts a wide spectrum of drug programs. The leads include: atherosclerosis, asthma, PDE4/vascular disease, schizophrenia, Type II diabetes, obesity, and heart attack/MI—all between discovery and Phase II.[300] On 11 May 2005, the *New York Times* released a story on the positive Phase II results of DG031, deCODE's lead heart attack/MI drug that is thought to inhibit a protein called FLAP. The *Times* stated that DG031 could "prove to be one of the first major drugs to emerge from the human genome project" and "[i]f the drug proves effective, Dr. Stefansson said, he expects that it could be taken as widely as the statin drugs."[301]

Conclusion

While other gene bank projects have gone out of their way to avoid the mistakes of Iceland, it is remarkable that the deCODE effort has been so successful. Some claim that decode took advantage of "a very different climate in Iceland" about issues like privacy and consent.[302] Others drew different lessons:

> First, a country's public attitude to technology does matter. Second, and just as important, given the right climate, public views can evolve. Efforts comparable to deCode's in the United States and the United Kingdom met similar fears and were either quickly shut down or, as in the case of

the U.K. Biobank, slow to get off the ground...To their credit, the people of Iceland dealt with the issues, compromised, and efficiently pushed ahead with what many now recognize as vitally important medical research. Perhaps it was a courage in the face of the unknown inherited from Viking ancestors.[303]

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[241] Lonely Planet, Ibid.
[242] Lonely Planet, ibid.
[243] Lonely Planet, ibid.
[244] Lonely Planet, ibid.
[245] Kunzig, R. Blood of the Vikings. *Discover* Chicago: Dec 1998. Vol 19, Iss. 12, p. 90-99.
[246] Enserink, M. Iceland OKs private health databank. *Science* Vol 283, iss 5398, p. 13. 1 Jan 1999.
[247] Thorgeirsdottir, S., Genes of a Nation: The Promotion of Iceland's Genetic Information. *Trames*, 2004, 8(58/53), 1/2, 178-191. Also available online at http://www.msu.edu/~hlinde/fab/genes.doc (accessed 8 May 2005). Referenced were:
Helgason, A., Hranfkelsson, B., Gulcher, J. R., Ward, R. and Stefánsson, K. (2003) "A Populationwide Coalescent Analysis of Icelandic Matrilineal and Patrilineal Genealogies: Evidence for a Faster Evolutionary Rate of mtDNA Lineages than Y Chromosomes". *American Journal of Human Genetics* 72, 1370–1388.

Helgason, A., Sigurðardóttir, S., Gulcher, J.R., Ward, R., and Stefánsson, K. (2000) "mtDNA and the Origin of the Icelanders: Deciphering Signals of Recent Population History". *American Journal of Human Genetics*, 66.
[248] See Árnsason, E. Genetic Heterogeneity of Icelanders. *Annals of Human Genetics* (2003) 67,5-16. The summary to this technical article reads:
Recently statements have been made about a special 'genetic homogeneity' of the Icelanders that are at variance with earlier work on blood groups and allozymes. To validate these claims an extensive reanalysis was undertaken of mtDNA variation by examining primary data from original sources on 26 European populations. The results show that Icelanders are among the most genetically heterogeneous Europeans by the mean number of nucleotide differences as well as by estimates of θ parameters of the neutral theory. The distribution of pairwise differences in general has the same shape as European populations and shows no evidence of bottlenecks of numbers in Iceland. The allelic frequency distribution of Iceland is relatively even with a large number of haplotypes at polymorphic frequencies contrasting with other countries. This is a signature of admixture during the founding or history of Iceland. Assumptions of models used to simulate number of haplotypes at sampling saturation for comparing populations are violated to different degrees by various countries. Anomalies identified in data in previous reports on Icelandic mtDNA variation appear to be due to errors in publicly accessible databases. This study demonstrates the importance of basing analyses on primary data so that errors are not propagated. Claims about special genetic homogeneity of Icelanders are not supported by evidence.
[249] Árnason, E. "Factual errors and racist undertones". Letter sent to the *New York Times,* February 1999. Quoted in Thorgeirsdottir, S., Genes of a Nation, ibid.
[250] Thorgeirsdottir, S., Genes of a Nation, ibid.
[251] Kunzig, R. Blood of the Vikings. Ibid.
[252] Lok, C. Translating Iceland's Genes into Medicine. *Technology Review.* Cambridge:Sep 2004. Vol. 107, Iss. 7, p. 58-64
[253] Overby, S. Iceland's dilemma: Privacy vs. progress. *CIO* Framingham:Jul 15, 2001. Vol. 14, Iss. 19, p. 78-85
[254] Kunzig, R. Blood of the Vikings. Ibid.
[255] Enserink, M. Iceland OKs private health databank, ibid.
[256] Gudmundsson, S. and Steinsson, K. Systemic lupus erythematosus in Iceland 1975 through 1984. A nationwide epidemiological study in an unselected population. *J Rheumatol.* 1990 Sep;17(9):1162-7.
[257] Thorlacius, S. et al. Population-based study of breast cancer in carriers of BRCA2 mutation. *Lancet* 1998; 352: 1337-39.
[258] Overby, S. Iceland's dilemma, ibid.
[259] Overby, S. Iceland's dilemma, ibid.
[260] Greely, H. Informed Consent and Other Ethical Issues in Human Population Genetics. *Annu. Rev. Genet.*2001. 35: 785-800.
[261] Decode Genetics Inc. SEC Form S-8, filed 19 July 2002.
[262] Kunzig, R. Blood of the Vikings. Ibid.

[263] Anonymous. Population, Inc. *Technology Review*, Cambridge: Apr 2001. Vol 104, Iss. 3, p. 50-55.
[264] Chadwick, R. The Icelandic database—do modern times need modern sagas? *British Medical Journal*. London: 14 Aug, 1999. Vol 319, Iss 7207, p. 441-444.
[265] Overby, S. Iceland's dilemma. Ibid. Also, Kunzig, R. Blood of the Vikings (ibid) names Roches and indicates that the collaboration will last for five years "to identify genes for 12 specific diseases: four of the brain (schizophrenia, anxiety disorder, Alzheimer's, and manicdepressive disorder), four cardiovascular diseases (heart attack, peripheral vascular disease, high blood pressure, and stroke), and four other diseases (osteoarthritis, osteoporosis, non-insulindependent diabetes , and emphysema). The agreement gives Roche the right to develop diagnostic tests and drugs based o nteh genes deCODE discovers; it also gives all Icelanders free access to those drugs and tests."
[266] Overby, S. Iceland's dilemma. Ibid.
[267] Lok, C. Translating Iceland's Genes into Medicine. Ibid.
[268] Naik, G. Decode, IBM Form Alliance to Market Gene Software. *Wall Street Journal*, 23 Jan 2003.
[269] Overby, S. Iceland's dilemma. Ibid.
[270] Overby, S. Iceland's dilemma. Ibid.
[271] Chadwick, R. The Icelandic database, ibid.
[272] Anonymous. Population, Inc. Ibid.
[273] Enserink, M. Iceland OKs private health databank, ibid.
[274] Decode Genetics Inc. SEC IPO Registration Statement. 13 July 2000.
[275] Overby, S. Iceland's dilemma, ibid.
[276] Decode Genetics Inc. SEC IPO Registration Statement. 13 July 2000.
[277] Ibid.
[278] Greely, H. Informed Consent, ibid.
[279] Ibid.
[280] A joint statement from deCODE genetics and the Icelandic Medical Association, dated 27 August 2001. Available online at http://www.decode.com/ (accessed 8 May 2005). The full text follows:

A joint statement from deCODE genetics and the Icelandic Medical Association

Negotiations between deCODE genetics and the Icelandic Medical Association, begun in February last year, have been concluded. The result is the accompanying joint statement, which will be signed in Reykjavik today. deCODE genetics and the board of the Icelandic Medical Association are very pleased that an agreement has been reached and hope that the mutual trust reflected in the joint statement will continue to guide their approach to all future matters of common importance:

Joint Statement of the Icelandic Medical Association and deCODE genetics on the Health Sector Database

I.

If information on a patient's health, contained in medical records and stored in healthcare institutions or by independent physicians, has been transferred to a Health Sector Database according to the legislation on such a Health Sector Database and the patient wishes that this information be deleted from the database, it shall be done immediately after the wish has been put forth.

The operator of a Health Sector Database shall develop methods to delete information from the database and pledges not to commence the transfer of health information into the database until they have been fully developed.

A demand for the deletion of a patient's health information from the Health Sector Database shall be addressed to the Medical Director, who shall see to it that the demand is implemented. deCODE genetics will pay the costs incurred in processing and executing such demands.

II.

The World Medical Association is an authority on medical ethics and has led in the drafting and implementation of internationally acknowledged rules on the ethics of science. deCODE genetics and the Board of the Icelandic Medical Association agree that when the policy of the Annual General Meeting of the World Medical Association on ethical considerations regarding health databases and individuals' health information in such databases has been issued, this policy shall be looked upon as guidelines for gathering, transferring and processing of information into Health Sector Databases in Iceland.

If necessary, both deCODE and the Board of the IMA will urge that amendments be made to the law on the Health Sector Database No. 139/1998 to ensure the law's conformity with these rules.

III.

The Board of the Icelandic Medical Association will recommend to Icelandic physicians to honour this statement and will present it at this year's Annual General Meeting of the Association for adoption.

Reykjavik, August 27 2001,
Dr Kari Stefansson
on behalf of deCODE genetics
Dr Sigurbjorn Sveinsson
on behalf of the Icelandic Medical Association
Dr Sigurdur Gudmundsson
Medical Director

[281] Will my newborn baby automatically go into the database? Parent-to-be Eidur Alfredsson asks the Director General of Public Health. Available online at http://www.mannvernd.is/english/news/ea2dgph.html (accessed 10 May 2005).
[282] Kunzig, R. Blood of the Vikings. Ibid.
[283] See http://www.mannvernd.is/
[284] Anonymous. Population, Inc. Ibid.
[285] Anonymous. Population, Inc. Ibid.
[286] Billings, P. Iceland, blood and science. *American Scientist*. May/Jun 1999. Vol 87, iss 3, p. 199-200.
[287] Decode Genetics Inc. SEC IPO Registration Statement. 13 July 2000
[288] Overby, S. Iceland's dilemma. Ibid.
[289] Overby, S. Iceland's dilemma. Ibid.
[290] Decode Genetics Inc. SEC IPO Registration Statement. 13 July 2000.
[291] Kunzig, R. Blood of the Vikings. Ibid.
[292] Greely, H. Informed Consent. Ibid.
[293] Decode Genetics Inc. SEC IPO Registration Statement. 13 July 2000.
[294] Kunzig, R. Blood of the Vikings. Ibid.
[295] See www.mannvernd.is, accessed 10 May 2005.
[296] Lok, C. Translating Iceland's Genes into Medicine. Ibid.
[297] Overby, S. Iceland's dilemma, ibid.
[298] Rotman, D. Getting the Whole Story. *Technology Review*. Vol 107, Iss. 7, p 7. Sep 2004.
[299] JP Morgan analyst report "deCODE and Merck sign sizable clinical trial deal." 27 Feb 2004.
[300] See http://www.decode.com/ (accessed 12 May 2005)
[301] Wade, N. Drug in test acts on gene tied to heart. *The New York Times*. 11 May 2005.
[302] Overby, S. Iceland's dilemma, ibid.
[303] Rotman, D. Getting the Whole Story, ibid.

Discussion

It is remarkable that Iceland's deCODE effort succeeded, despite enormous international criticism and scrutiny. In contrast, other programs like the biobanks in the UK, Estonia and Sweden made deliberate efforts to ensure informed consent and engage in communication with the public. So why is it that some projects that put great effort into openness and ensuring privacy failed, while Iceland, which was thought to disregard individual liberty, has done so well? Unfortunately, we cannot answer this question directly due to insufficient data. However, we will attempt to distill patterns from the data gathered.

It seems that a number of factors are necessary, but not sufficient, for the eventual success of a biobank. That is, their presence does not guarantee success, but their absence destines the effort for failure.

Contractual Elements

Strong measures for maintaining confidentiality and the informed nature of consent were (with the exception of deCODE's access to healthcare records) universally implemented. This seems necessary in a world of instant electronic communication. While health insurance concerns may have been less of an issue for the populations involved because of their universal health care, people still feared of negative repercussions that genetic testing might have on their life or disability insurance, or on their employment. Confidentiality and consent, at least of genetic information, is therefore essential for any population study.

Clarity of Intellectual Property (IP) is a necessary-but-not-sufficient condition for biobank success. In most of the cases, it was clear that the intellectual property gained from tissue samples and its resulting data belonged to the bank and not to the donor (there was heterogeneity among the cases, however, in whether the donor would have access to—but not ownership of--her own data). Yet, the Sweden/Uman case shows. Hallmans, a scientist who was involved in creating the bank there, objects to the commercial nature of the endeavor. Yet, IP is the tool he uses to hold up the effort—thanks to an obscure "teacher exception" to patents that may or may not reward him some say over how the IP is used. A protracted court battle has ensued. We argue, though, that this situation came about not because of the commercial nature of the Uman and the biobank (though that was the precipitating cause), but because IP issues were either ignored when setting up the bank or because the system was inherently difficult to manage within.

Organizational Strucuture & Funding

There is insufficient evidence to determine whether the organizational structure is such a factor; logically, it seems not to be. There were a number of types of structures present: Newfoundland did not have any direct public involvement or government sponsorship of its bank; it was run as a private effort only, much like deCODE. Uman in Sweden was an intermediate example. It was commercial, but the majority of shares were owned by government and not-for-profit institutions. Estonia and the UK, on the other hand, were public-private partnerships set up through not-for-profit companies. A hypothesis such as "the success of a biobank effort is inversely proportional to the degree of direct commercial involvement" is patently false, as proven by deCODE. And yet, degree of government involvement does not correlate well with either success or failure. Newfoundland had probably the least active public sector role: the government talked a bit about setting general consent and privacy requirements, but left Newfound to struggle on their own. And, though still alive, they remain a tiny, struggling company. The Estonian government, on the other hand, was looking to build a national champion along the lines of Finland's Nokia. Despite support from the highest levels of government, the program failed. The role for government (whether national or local), therefore, seems to be less about partnering directly with a company (though they certainly did this in Iceland) as it is the proper forum for public debate to educate and help the populace clarify their values around very tricky issues. The Iceland approach, then, differs greatly from the UK government-sponsored approach. In the UK, the MRC and Department of Health provided funding for the project, but most of the community consultation strategy felt more like market research. True dialog and airing of views was replaced by polls and focus groups, the results of which were mined and used to guide the discourse of biobank officials. According to observers and scholars who have commented upon the process, people felt like they were being sold to and despised it. The presence of commercial interests made this all the more worrisome because it violated the trust that was the bedrock of gift exchange. Why give a gift freely when you feel patronized and don't trust the motivations of the organizations who are asking for your donation? Thus it is not only companies that can be unsuccessful in shifting the nature of exchange from individual gifts to more orchestrated, commercial activities that are part of an agenda of national competitiveness.

Even with a fair bit of trust, the most secure encryption efforts, efforts can still fail if not well-funded. Estonia had been criticized for engaging in top-down communication that harkened back to the paternalistic ways of the old USSR. For whatever reason, public support of the effort was high. Yet the effort failed because of the stage of the project given its funding environment (post-doc.com market crash caused venture capitalists to tighten outlays). EGeen was asking financiers to fund the development of

this bank from scratch with minimal infrastructure already in place. It had only a promise of a product years away.

Compare this situation with deCODE. While that effort also took building, Stefanson was starting far ahead of the Estonian effort. He spent much of his life in the United States, home to most venture capital money, and had burnished his credentials and contacts at Harvard. His country's population was only a fraction of the size of Estonia's, and it already had an established healthcare system, genealogies, and medical records. While deCODE built significant capabilities to manage data, it utilized much of this existing infrastructure. For these and probably other reasons, deCODE was able to raise hundreds of millions of dollars through VC's, pharmaceutical partnerships, and eventually an IPO. EGeen ran out of gas with only a few million dollars, and the Estonian government did not have the resources or will to save it.

Conclusions

While considerably more study is needed to understand the complex factors influencing the outcome of population genetic projects, this study allows us to form several hypotheses for future investigation:

- Efforts are doomed to fail if proper funding and IP issues are not sorted out ahead of time.
- Commercial involvement and gift exchange are not mutually exclusive, and are in fact complementary in large studies. In other words, success is not about the amount of monetary compensation per se but rather considerations of appropriate rewards, recompense to the community etc. Commercial interests, however, need to be cognizant that gift exchange comes with expectations, of which trust is paramount.
- Studies will be most successful after true democratic discussions (best held by governments or community leaders) that help establish rules of the game that are acceptable to the culture of target populations. While not all will agree with the outcome from a public debate, such an outcome is likely to be more palpable than commercial-like marketing—especially when the population is already concerned about potentially deleterious effects from commercial involvement in healthcare and genomics.
- A corollary to the above (as shown by the deCODE example) is that values may not be universal, and hence what works in one culture may not work in another. Yet there is also a standard of informed consent necessary in any culture.

We as a global society must find a way to simultaneously embrace the revolutionary promise of personalized medicine while protecting the sanctity and well-being of groups and individuals, especially the most vulnerable in society. Governments, the medical community, academics and individuals all have important roles to play and only together can manage the creative tension between gift and commercial exchange.

Appendix F: Comparison of Six Biobanks Across Key Variables

	Biobank Structure	Funding Sources	Target study enrollment (current)	Anonymization method	Access to own results?	Community consultation strategy	Government cooperation	Commercial Involvement	Consent	HC system type	IP handling	Pmt to Physicians	Population type (heterog/homog)	Nature of early experience	Results
UK Biobank	Company Limited by Guarantee & Registered Charity; Coordinating Center with six regional centers	MRC & Department of Health, Wellcome Trust	500,000 (entering small pilot study)	Coding--detail not clear	No	Extensive communication: focus groups, surveys, etc.	Yes, through MRC & Dep of Health	None initially, though results will be licensed	Blanket informed consent. Can always withdraw	Gov't run NHS	Owned by Biobank	Handled by NHS	Heterog.	Extensive research experience	Slow start due to public opposition
Quebec/CARTaGENE	?	CARTaGENE funding not clear (from Genome Canada?); Genizon/Galileo from private investors	50-60k	double-coded by the Quebec Health Insurance Board (RAMQ) and by CARTaGENE	Yes, through code	Two-way partnership approach	CARTaGENE funding?	Genizon/ Galileo has own recruitment efforts. Not clear if CARTaGENE shares data with it, or vice-versa.	Informed consent (details unavailable).	Government Payor	Not clear	?	Homog.	Some prior research (e.g. Quebec Family Study). CGAT cut from budget in 1996.	Genizon announced progress in psoriasis & other efforts; CARTaGENE mothballed/ \restructuring
Newfoundland/Newfound Genomics	No public biobank; Newfound Genomics only	Private	?	Not clear	Probably not	?	No	Exclusively commercial	Informed consent (details unavailable).	Government Payor	Held by Newfound Genomics	?	Homog.	Exploited by 'helicopter genetics'	Company surviving
Estonia	EGPF (non-profit) creates & manages database. Private EGeen is exlusive commerical licensee.	Mostly through EGeen, though gov't covered some gaps	1 mm initially, scaled back to 100 k (10k pilot study completed)	Coded, info disclosed only for groups >=5	Yes	Top-down	EGPF created by Human Genes Research Act (of parliament)	Yes, explicitly	Informed consent (details unavailable).	Government Payor	Property of gene bank	Yes, greatly exceeding std pmt	Moderately heterog.	Soviet legacy, though Estonia was center of bio rsrch in USSR	EGeen stopped funding; EGPF ran out of funding
Sweden (Vasterbotten)/Uman	UmanGenomics had exclusive commercial license to Biobank	Government/university with minority shareholders in Uman	approx. 85k (85k)	Coded, key kept by public institution	?	?	Biobank established by county/city council.	Uman Genomics (51% owned by health dept & university)	Informed consent	Government Payor	Jointly owned by univ. inventor & Uman	?	Homog.	Umea Medical Biobank amd Vasterbotten Intervention Program (VIP)	Mothballed after univ. founder objected to commercial nature
Iceland/deCODE	Exclusive commercial license for deCODE to build & operate	Extensive private money, IPO	Entire population of 280k (>110k)	Coded	No	Top-down	National law enacted	deCODE	Phenotype is opt-out only; genotype is opt-in informed consent	Government Payor	Owned by deCODE	?	Homog.	Prior nation-wide studies for specific diseases	deCODE very successful; high popular support