

CASE STUDIES

CASE STUDY 2: Estonia

Background

In October 1999, geneticists in Estonia proposed plans for construction of a national genetic database of the population of Estonia. The database would be owned by a foundation set up by the Estonian government, with capital supplied by commercial entities that would then have access to the data for research purposes. Subsequently the project was approved, and the government also passed a Human Genome Research Act (HRGA), which regulates collection, storage and use of the tissue samples and data in the project. Approximately 1 million blood samples and detailed medical histories are to be solicited from among the country's 1.4 million residents; by January 2004, about 10,000 donors had given samples. In contrast to other national genetics projects, for example, Iceland and Tonga, there was little opposition on the part of the Estonian public, although there were critics among the medical establishment.

The Baltic state of Estonia achieved independence from the Soviet Union in 1991. While Estonia has had a long history of domination by more powerful neighbors, including Sweden, Germany and Russia/USSR, it has also enjoyed periods of relative independence and national sovereignty, preservation of its culture and language, and commitment to democratic governance. Estonia struggled for independence during the Russian revolutionary period, and in 1920, the new Republic of Estonia signed a treaty with the Soviet Union, establishing its sovereignty. A parliamentary government was formed and economic and political reforms took place, including land reform, and guarantees of cultural autonomy for minority groups. In 1939, Estonia was occupied again by the Soviets; deportation and repression occurred under the Stalinist regime, which gave way to more moderate governance in the perestroika period. In 1990, Estonia held free elections for its Supreme Soviet, and restored its original name as the Republic of Estonia, gaining formal independent status in 1991.

In 1992, Estonian voters approved the country's draft constitution and implementation act, establishing a parliamentary government headed by a president and prime minister. The Estonian parliament is chosen by direct election, and currently representing several active Estonian political parties. Estonia has instituted free market reforms and privatization of state-owned enterprises from the Soviet era and has enjoyed good economic growth; it currently has a per capita GDP of \$4720.¹ The republic has friendly diplomatic and trade relations with Western Europe and the US, and is slated to join the EU in May 2004.

The population of Estonia is 65% Estonian, and 28% Russian, with smaller numbers of other ethnic groups.² The country's long history of occupation by different nations means that the population is genetically heterogeneous, as are many other populations in Western Europe and North America. Estonians have universal access to health care, have life expectancy of 69 years for men, and 74 year for women, (slightly lower than that of their Western European neighbors) and are generally well educated. However, not all the news is good: education-related disparities in mortality are increasing and the country has a growing AIDS epidemic.³ Health care reforms are ongoing, as the centralized Soviet system is being replaced by a new public health infrastructure.

The Project

The project, spearheaded by a geneticist at Tartu University, is designed to collect about one million samples and medical histories from individuals over five years. The Estonian project requires active informed consent for each sample and medical history included in the database. Donors can withdraw personal information from the database, but cannot withdraw samples once they have been given, unless confidentiality agreements have been breached, in which case

samples or data must be destroyed if the donor requests. The project is governed by the HGRA, which was drafted by an interdisciplinary Estonian group of scientists, lawyers, ethicists, physicians, and politicians. Under the HGRA, individuals who participate in the project and give blood samples and medical histories waive their ownership and transfer it to the Genome Project, which is governed by specific rules regarding informed consent, coding and handling of samples and data, and transfer to other parties for research. Samples are to be coded, but not anonymized, meaning that genetic information or research results about an individual can be returned to them, if they so desire.⁴

Under the HGRA, ownership of samples is distinguished from intellectual property claims. The HGRA defines the Genome project as the owners only of the tissues and genetic data; in contrast, “elaborate” genetic data—presumably research findings based on use of the database—are not owned by the project and might be patented by researchers or commercial entities.⁵ Commercial entities and outside researchers can pay for access to the database through a for-profit subsidiary of the EGF. Publicly-supported researchers in the country would have access at no cost or for a minimal fee.

The Estonian Genome Foundation (EGF) has a 2.5% share in the commercial entity. The commercial subsidiary will pay an annual payment of \$300,000 euros to the foundation plus 0.5% of profits, which are not expected in the short term. The estimated cost of the project is about 1,000 euros per participant; this cost will also be paid by the commercial entity. Patents applied for by the commercial subsidiary will be co-owned by the commercial entity and the foundation, which will receive 3% of turnover based on transfer of IP rights.

The genetic heterogeneity of the population of Estonia increases the likelihood that findings relating genetic polymorphisms to health outcomes will be generalisable to other populations. Some investors are interested in studying the relationship between single nucleotide polymorphisms (SNPs) and drug metabolism—projects that would be well served by a genetically diverse database.

Since much of the DNA analysis will be performed within the country, the project is expected to boost the country’s biotechnology capacity and local research efforts. Project enthusiasts are hoping that growing research capacity will attract more outside funding for the nation’s scientists.

By January 2004, donations and commercial investment in the project had reached 55 million kroons, while Estonian government investment was less than 2 million. A US-based company set up for the project is the commercial entity handling most of the investments, and has exclusive rights to use or rent the database for 25 years. The company decided to focus initial research on specific diseases such as diabetes, heart disease and rheumatoid arthritis, rather than compiling a complete database of the population. In addition, the general medical history collected from the family practitioners in the project to date were considered insufficient to get research value from the genetic information, and plans were made to obtain detailed information from medical specialists. The head of information for the EGF commented, “The idea of the Estonian Genome Project has been—and still is—to create a database that would include the health and gene data of the Estonian population... Today investors and [the company] are more interested in collecting the data by disease groups. But this is not exactly in accordance with the idea of goals of the gene bank, as declared in the Human Genes Research Act.” However, there was dispute among officials at the EGF concerning this point. In response to concerns of the CEO of the EGF that the commercial entity was pursuing inappropriate research goals, the Estonian government committed an additional 4 million kroons to the project, and discussed further investment by outside donors such as the Wellcome Trust.⁶ More recently, concerns at the foundation about the direction of the research were resolved; in April 2004 the annual budget agreement between the [the company] and EGF was completed as originally planned, [the company] paying 26 million kroons to the EGF, along with plans for gathering more detailed medical records for the next 5000 gene donors this year.

Critics and supporters.

One of the few publicly outspoken critics of the program, a physician in Tallinn, believes that the country should focus on more immediate public health concerns rather than “expensive high-tech endeavors”.⁷ Others have commented that this view reflects a misunderstanding of the project, since, after an initial contribution of \$100,000, no public funds are being spent to establish the database. This physician also expressed concern that Estonians, used to Soviet-style government, would be unlikely to question government-sponsored research projects that they barely understood.⁸ Other commentators remarked that Estonian physicians also might be unlikely to question government authorities, in the wake of the Soviet era; however many Estonians resent this view of their capacity for autonomous decision-making.

Some commentators have noted that there is little negative public reaction in Estonia. “It has been hard to have a debate with no real opposition around” remarked an editor of the *The Estonian Daily* in 2000.⁹ In a 2003 poll, 40% of Estonians supported the project, 2% were against it, and 30% would wait for the project to develop before joining; 19% said they needed more information.¹⁰ Some survey data also indicates that members of the public may have misconceptions about potential benefits of the project, such as the potential to cure many diseases or provide free drugs.¹¹ In a March 2003 survey by a marketing research firm, more than 75% of 500 Estonians surveyed thought the project was designed to benefit both the state and the people of the country.

In fact, some stakeholders believe that direct health benefits will result for the Estonian population. “The potential for a return for the health care system is substantial” commented the CEO of a biotech company in Texas. The Estonian geneticist who conceived of the project believes the information will allow medical treatments to be customized: “Medical treatment will increasingly be tailored to specific genotypes, and this database would allow individuals to gain knowledge of disease risks and to receive the most effective medication.”¹²

There has been little discussion of privacy risks for individual donors. One journalist has commented that Estonians seemed relatively unconcerned about the issue, “While the ethical dilemmas surrounding genetic screening have been debated at length in Britain and other European countries, Estonians don’t seem to be aware of these problems.”¹³ The EGF website addresses this topic in terms of confidentiality procedures, including coding of samples, separation of personal from genetic data, and storage of computer files unconnected to networks.

Combined Discussion Questions, for Tonga and Estonia

Genetic information, somewhat paradoxically, is both a shared heritage among humans-- even more so among those of common ancestry-- and also an intensely private matter. Decisions about gathering data on genetic profiles of groups raises simultaneously the issues of group ownership and of individual consent, and the potential tensions between these claims.

Ownership claims

- Does a group of people (such as the residents of Estonia or Tonga) have collective ownership of, or collective interest in, their genetic heritage? If so, how could this ownership or interest be described, both in terms of what ‘genetic heritage’ means and in terms of how the population of ‘owners’ might be defined?
- Would some kind of collective claim or ownership have implications for individuals who wish to join a research project without an agreement established with wide discussion and general agreement among Tongan community members?
- In cases where group leaders, such as national governments, make decisions to engage in national genetics projects, are the rights or interests of individuals who oppose the

project subsumed by those who support it? Are special informed consent procedures needed to take account of family issues in genetic research with large populations?

Governance and Benefit-Sharing

Commercial benefits of genetic research are difficult to predict, especially in the short term. In cases where benefit-sharing agreements are constructed around potential commercial profits, these benefits may not emerge at all in the short- or medium-term. There are also questions about the form and disbursement of benefits to populations, for example as up-front payments or percentage of future royalties that may be dedicated to projects or programs, or as free provision of commercial products of research resulting from the genetic information.

Genetic research is often described as holding a promise of increased understanding of multifactorial disease, and better health care for individuals. Some commentators are concerned that these promises are not balanced in relation to more immediate public health concerns for populations that participate in genetic research. In some cases there are expected benefits from the results of genetic research that may be applicable to specific health problems. In the Tongan case, some commentators believed that unraveling the genetic basis of diabetes and obesity would be critical in addressing their increased incidence in Tonga. Experts note that it is a relatively recent phenomenon, and environmental conditions such as Western diet and decreased exercise probably play a key role, as well as genetic background. Some public health experts believe that focusing on genetic research in relation to diabetes and obesity might be inappropriate, in comparison to preventative approaches or use of existing treatment modalities.

Some observers are concerned that it is risky to return results of genetics studies to individuals when there is no evidence for making medical decisions based on the new genetic information. This risk might be higher in situations where medical records are linked to genetic analysis. There is also widespread concern about privacy in genetic research, in particular, breaches of privacy that might result in stigma or discrimination, such as denial of employment or insurance. At the same time, there is little documented evidence of harms that have arisen as a result of disclosure of genetic information gathered in research. Some individuals associate genetic research with fears about manipulation of the genome and devaluation of the natural life of human beings. Others claim that some or all of these fears are unwarranted, and that genetic research is inherently no more or less risky than other kinds of non-invasive biomedical research.

- In the two cases described, historical context, governance and decision-making regarding genetic databases at the national level were quite distinct. What ethical concerns arise concerning the ability of national governments to negotiate and decide agreements for genetic research concerning their populations? Can decision-makers be unduly swayed by the potential for commercial profit or valuable collaboration with scientific groups? The islands of Tonga have a history of relationships with colonial powers, including current economic dependence on more industrialized nations. Is this an interesting footnote, or a substantive concern in the negotiation of agreements with foreign companies?
- Would it have made any difference if the genetic research project was carried out by a non-profit entity, as opposed to a for-profit commercial entity? Non-profits can also acquire patents to DNA sequences or products derived from research on specific genes. Do the overall goals of the research matter?
- Are risks of research and potential benefits characterized adequately and analysed as part of the decision-making process at the national level? Was there sufficient public discussion of potential risks or benefits in the two cases? How can benefit-sharing arrangements be evaluated in terms of fairness, transparency, and responsiveness to national needs? How can it be determined that benefits that may accrue to a body or governmental organization in the country can serve the interests of the population?

Bibliography

¹ U.S. Department of State. Background note: Estonia. From website: <http://www.state.gov/r/pa/ei/bgn/5377.htm>

² Ibid

³ Leinsalu M, Vagero D, Kunst AE. Estonia 1989-2000: enormous increase in mortality differences by education. *Int J Epidemiol*. 2003 Dec;32(6):1081-7.

⁴ Human Genes Research Act (HGRA). RT I 2000, 104, 685 (2000).

⁵ Ibid

⁶ Petrone J. US investors rethinking genome project. *The Baltic Times*. 2004 Jan 29. From website: <http://www.genomics.ee/index.php?lang=eng&show=16&nid=224>.

⁷ Frank L. Storm brews over gene bank of Estonian population. *Science*. 1999 Nov 12;286(5443):1262-3.

⁸ Ibid.

⁹ Frank L. Population genetics. Estonia prepares for national DNA database. *Science*. 200 Oct 6;290(5489):31.

¹⁰ Breithaupt, H. Pioneers in medicine. *EMBO reports*. 2003 Nov 15;4(11):1019-21.

¹¹ Ants Nomper, a lawyer at Raidla & Partners in Tallin, Estonia asserts: "Some surveys have shown that a big proportion of potential gene donors are driven by incorrect imaginations, such as genetics will cure every diseases and there will be new drugs available for free." Breithaupt, H. Pioneers in medicine. *EMBO reports*. 2003 Nov 15;4(11):1021.

¹² Frank L. Storm brews over gene bank of Estonian population. *Science*. 1999 Nov 12;286(5443):1262-3.

¹³ Gross M. Estonia sells its gene pool. *The Guardian*. 2000 Nov 9.

COMBINED DISCUSSION FOR ESTONIA AND TONGA

Rapporteur:

I would first like to point out that the discussion was particularly heated. I encountered a few problems in controlling the debate. Each participant expressed his/her personal view of the case at hand. In the absence of the main interveners in both cases, we listed a certain number of points that we would like to submit to Rev. Simote Yea and Dr Ants Nomper for their consideration.

We started out by reflecting on the fundamental differences that exist between Estonia and Tonga, as well as the reasons behind Tonga's refusal to participate in the NDTI, while Estonia accepted to participate.

The discussion heated up as soon as the question of religion was brought forward. The church is of considerable importance in Tonga. It offsets the absence of certain institutions, ethics committees are an example. In contrast, Estonia, a former Soviet bloc country, has a less significant religious background. The authority of the State is respected by the population.

The perception of science is another dividing line between these two countries. Estonia has a relationship with science that goes far back. This tiny little country holds internationally renowned, scientific institutions: the Estonian population seems to be aware of scientific imperatives and actively participates in experiments. Conversely, we believe that the inhabitants of Tonga have a very remote relationship with science.

Strong ideas came out of this discussion which, I repeat, was heated to say the least. Let us just say that, whatever our perception of science, the absence of respect for those involved results in the mistrust of innovation. It is vital and urgent that we question the differences between the benefits and profit. The next few interveners will develop this point.

Rapporteur:

Our group discussed the Estonian benefit sharing arrangement and decided that it was not fair, as the shareholding is too small and the level of profit-sharing with the community, at around 3%, is too low.

On the question of community consent, it was felt that in Estonia, the public agreed as they were approached in a way that encouraged them to support the project. In Tonga, the public was alienated by the approach which was taken but, in any case, would have been less likely to be supportive, given their moral attitudes.

We could not agree whether the economic philosophy of the groups involved is an important factor as it is difficult to draw an accurate dividing line between for-profit companies and non-profit organisations.

Rapporteur:

A number of interesting issues were discussed in our group. First, we considered how the governance process in Estonia and Tonga affected the outcome of the project. It was questioned whether governments should be allowed to make such decisions on the part of the population and whether, in Estonia, the public genuinely understood the nature of the project prior to giving their consent. Where issues of stigmatisation or exploitation could arise from individuals, families or groups being identified as having a defect, it was felt that consent should be given at individual or community level and not simply at a national level.

Intellectual property rights have an important link with risks and benefits. We discussed the inequalities which exist between developed and developing countries, particularly in terms of infrastructure and political background. The political situation of a country has a significant impact on the creation of benefit sharing agreements, on the potential for exploitation and stigmatisation, and on the question of whether data should be owned on an individual or a collective basis. Although consensus exists that the interests of the people involved must be considered; this does not necessarily extend to collective input into research subjects or genuine collective consent.

The long-term potential benefits of gene databases were considered. It was noted that, although these databases can be very beneficial, they can also be extremely dangerous. It was questioned whether genetic studies should be a priority in countries where basic problems such as AIDS, political turmoil, and access to primary healthcare remain unsolved.

Rapporteur:

During our discussion of ownership claims, it was noted that the discussion paper uses the phrase "collective interest in genetic heritage". We felt that the notions of genetic identity and property should be associated, so that the property rights of a group of individuals would be governed by their collective interest in their genetic identity. In this way, a group could not object to some individuals choosing to participate in a genetic study. Given that losses might be experienced by those who did not take part, two possible safeguards were suggested. The first proposes that any benefits which were obtained would be shared by everyone with the same genetic identity. The second proposes that a minimum level of consensus be agreed. Individual property rights are important but it is important that there is a collective sharing of the genetic interest. Words like 'community' and 'collective' are being used very loosely at present and might benefit from tighter definitions.

It is important that governmental commitment is obtained once a study is proposed. The perception which a population has of science was also felt to be an important factor. In some countries science and technology are viewed as having a positive impact but this attitude is not shared throughout the world.

Somewhat provocatively, it was suggested that democracy should be a pre-condition for these kinds of studies. This would, of course, require a significant amount of debate in order to determine the quality of democracy and the quality of mandate which would be acceptable.

The final proposal of the group is that discussions be held to debate the creation of an accreditation process for research companies. Drawing on the analogy of the human rights movement, it was felt that it would be beneficial to conduct ethical auditing, which would allow communities to feel confident that they were negotiating with a responsible body. We believe that this could be implemented as a concrete process.

Chairperson:

Thank you to all those who chaired and reported from the workshops. We shall now take brief questions and comments relating to ownership.

Comment:

In Malawi, genetics is considered to be a private thing. However, it is acknowledged that as the results of genetic research may affect a third person, it is not entirely private but also has public aspects. When the risks of an individual's actions can have an impact on a third person, the benefits of those actions should also be shared with the third party. The individual can benefit from collective ownership but when risks go beyond the individual realm, benefits must also go beyond the individual realm. In such a situation, individual autonomy can no longer take precedence.

Comment:

I am wondering about the guarantees that could preserve the countries of the South from their current feelings of anxiety. I have two questions.

First of all, should we contemplate the implementation of a sort of international solidarity in order to offset the issue of risk benefits in terms of research and good practices?

My second question deals with the concept of vulnerability. The case study showed that situations are different from one country to another. So, should controversies and contradictions be managed by project or by country? The country approach seems ineffective to me since, for example, it clashes with religious obstacles. In other words, the concept of informed consent and the distinctiveness of the individualism necessary for a research protocol would not be considered in anticipation of a benefit for the collective good.

Lastly, it seems to me that we cannot take the stigmatization associated with vulnerability-defined as a predisposition to an abnormality and not a pathology -as a criterion: the biological, cultural and psychological diversity, as well as the consent of the subject must be deontological factors rather than commercial ones.

Comment:

Although we have talked about the collective ownership of the community and of individuals, we must remember that the company which collects the data also wants to own it and control the use of this information.

Comment:

In my opinion, the whole concept of ownership is not appropriate in this context and that a different approach should be considered.

Comment:

Would it not be appropriate to clearly distinguish between the benefits issue and the question of added value? Benefits oppose risks while added values are economic elements. This semantic distinction is essential: maybe you could clarify this.

Chairperson:

Thank you. Our panel members, Dr Annts omper and the Rev. Vea, will now respond.

Comment:

The issue of ownership affects the many different levels of community which are involved in collective ownership. It also applies to the question of entitlement to genetic heritage, that is, the ownership rights of those individuals who inherit the genetic ancestry concerned. The wide-ranging impact of genetic knowledge must be considered, particularly as whole families may be stigmatised or discriminated against as a result of research identifying one member as having a disease. This situation has already arisen with AIDS and HN. Decisions regarding collective claims must be taken in the context of collective genetic heritage and must therefore consider the whole community as well as the individual. When the wider national community is implicated, decisions must benefit the whole population and not simply the company or the government.

The important question of international solidarity gave rise to our proposal for an auditing and accreditation programme for companies which want to conduct research, whether in developing or developed countries. These companies must also be considered when discussing collective and individual ownership as, in the end; they own both the genes and the benefits. Ownership and benefits are so closely inter-related that a joint approach must be taken when discussing them.

Comment:

The comment regarding the 25-year ownership of tissue and data highlights an important misconception about the Estonian database. All of the data and tissue samples stored in the genome database are entirely owned by a specially created foundation, which is controlled by the Estonian state. While commercial companies can use the data and tissue, they do not, under any circumstances, have ownership of it.

Chairperson:

Thank you very much. Unfortunately, we do not have time for questions on governance and benefit sharing, although I am sure that you are very keen to exchange views on these subjects. I would like to thank the speakers and other participants for their contributions this morning, which have highlighted many important points and which, I am sure, will be the focus of further discussion during the Forum.