"I think that as we move forward in this realm, it is a certainty that everybody's sensitivities are going to be stepped upon by someone."

occur if parents were allowed to choose the sex of their children. An absence of bias is not the only reason: "PGD is so inconvenient and so expensive that it will have no impact on the overall distribution of sex ratios anywhere in the world. It is not a practical technique for large-scale sex selection," Caplan said. However, other countries, where cultural and social traditions dictate that sons are more valuable than daughters, might not be so unbiased. The possibility of sex selection has therefore raised the question of whether it is hypocritical to advocate it in the West, while condemning countries such as India and China for essentially doing the same thing, although by more drastic means. "To me, those are larger social issues that are not best dealt with by trying to regulate the technology itself," Stock said. Dahl agrees that this question must be left to each country to deal with: "We cannot punish the people of our countries for the crimes committed in another country." Baldwin said, "the issue of what kind of example we set in the area of sex selection is an important one, though, equally, we in the 'west' should not arrogantly assume that our policies are right for everyone. There is a delicate balance to be struck in this area."

There are fears that PGD will eventually be used to select for non-medical traits such as intelligence, appearance and physical prowess, which concerns both advocates and opponents. Referring to his surveys in the UK and Germany, Dahl noted that this should not be overestimated. Of the small proportion of people who would use sex selection, an even smaller subset would use genetic diagnosis techniques to select for other traits. "I think the reference to the slippery slope presupposes something that's simply not right," he said. Hughes also believes that widespread selection of non-medical traits is unlikely, but for different reasons. "No one in their right mind would go through IVF technology if they didn't have to. You're not going to do this for a trivial reason." But even if the practice does not become widespread, Stock admitted, "I think that as we move forward in this realm, it is a certainty that everybody's sensitivities are going to be stepped upon by someone." He stressed, however, that a few

troublesome cases do not necessarily warrant strict regulations. Hughes agreed, "You can have a Domsday kind of attitude about it or you can say let's move forward in a responsible careful way, and evaluate and make sure that it's used properly."

Because PGD is a new technology in reproductive medicine, there are additional concerns about its safety and about its legal and commercial implications. PGD results are tracked in the UK, but private clinics in the USA are under no obligation to record their successes and failures. Across Europe, the European Society of Human Reproduction and Embryology (ESHRE) has created a PGD consortium to monitor its use and to produce guidelines and recommendations. But participation in the ESHRE's assessment is purely voluntary. In the meantime, mistakes in PGD have been publicized, with at least one fetus being found to contain the mutated gene that it was originally selected against; in a litigious country like the USA, the legal repercussions could be extensive. "I think you will move towards various kinds of wrongful birth suits and things of that sort," Stock said, but cautioned that such lawsuits will be as likely outside the USA as within. Caplan worries more about what social and economic pressures will do to the future of PGD and the

selection of non-medical traits. "Those pressures combined with aggressive marketing and advertising are what I worry about the most with respect to future genetic testing of gametes and embryos," he admitted.

"It's helping couples build healthy families, and what could be better than that?"

Given the difficulties involved in IVF, PGD will probably never become a standard service for prospective parents but will be reserved for individual cases in the most need. Hughes even hopes that one day it will be obsolete. As he pointed out, 11 years ago when PGD was first used, children with CF never had to worry about passing down the gene—they did not live long enough to have children. But now, modern pharmaceuticals and medical treatments mean that those suffering from CF live much longer. "Today's devastating diseases are hopefully tomorrow's cures and that's where we need to be focused," he said. In the meantime, "it's helping couples build healthy families, and what could be better than that?"

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Pioneers in medicine

Small countries are taking big steps towards improved genetics-based research and health care with the creation of population databanks

Sometimes revolutions begin in the most unlikely of places. Iceland is a piece of volcanic rock in the middle of the Atlantic Ocean, inhabited by less than 300,000 people. Estonia is now the easternmost outpost of the European Union, after an overwhelming majority of its people voted on 14 September to join the EU. The country only gained its independence from the former Soviet Union in 1991, and the consequences of Soviet rule are still reverberating. But both countries are leading the way in the next revolution in medicine by establishing DNA and health databases of their populations, something that most larger countries have not yet begun to consider.

"Many people are talking about population genetics, but you in Estonia are doing it," said John Norton, Director and CEO of the UK Biobank Project, at the Gene Forum 2003 conference in Tartu, Estonia, this September. In fact, it seems to be easier for smaller countries, such as Iceland and Estonia, to go ahead with such initiatives. "Establishing a database is of course easier in Estonia with its small population [of 1.4 million people]," agreed Arvo Tikk, chairman of the Ethics Committee of the Estonian Genome Project (EGP) Foundation, not only for logistical reasons but also because it is easier to convince the public, and to adapt the laws and regulations.

As of mid-September, deCODE, the private company that is operating the Icelandic genome and health databases, had collected genetic data for more than 100,000 Icelanders. The EGP finished its pilot phase in March this year and since then has collected biological samples and health data from more than 4,000 Estonians. The aim of both projects is the same, but the similarities end there. deCODE is a high-tech company based in Iceland's capital, Reykjavik, with more than 600 employees and state-of-the-art computing and sequencing facilities that allow them to genotype up to 35 million samples per month. The EGP is based in Tartu, Estonia's second largest city, and housed in a former cake factory near the biological faculty of Tartu University. Inside, a handful of employees accept the incoming samples, health data sheets and consent forms, and process the blood samples manually to extract DNA, plasma and leukocytes to be stored in liquid nitrogen. The legal setup for both projects is also different. deCODE is authorized by the Icelandic government, whereas the EGP is an independent institution ruled by Estonia's Human Genome Research Act (HGRA). Regardless of the differences in legal regulations, technical sophistication and sheer size, Iceland and Estonia are both pioneering a revolution in health care towards genome-based medicine. As such, they might very well serve as examples for other countries.

Probably the most striking feature of those involved with the EGP is their apparent willingness to make do with what they have to make it a success. The laboratory may be missing the sophisticated instrumentation that one would expect from a similar facility in a richer Western country, but it is definitely rich with the excitement of being a pioneer and with the keenness to improvise and solve problems. Samples and consent forms are taken by physicians from nearly all over Estonia and are delivered to the central laboratory by a private courier service that usually transports cash. From the time that a physician confirms that he has taken a blood sample, the clock starts ticking, as the software allows only 48 hours before samples and consent form must arrive in Tartu. The most common error is that physicians forget to sign the consent form, which means that the blood sample is not accepted until

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the form is returned to the doctor for signing. As Dagní Krinka, head of the laboratory, recollected, in one case, a consent form was redelivered by the courier service after 47 hours and 30 minutes—the driver had to run a couple of red lights to make it in time. So far they have not lost a single sample, she proudly claimed. On arrival at the laboratory, the blood samples are recoded to make them anonymous—the keys are stored in a computer in a safe room to which only a handful of people have access—and processed immediately. As Krinka said, their goal is to extract at least 1 µg of DNA from the blood samples, and this is much easier in the winter when many people are sick and have more leukocytes in their blood. "I don't like the summer," she commented. At the time of writing, most regions in Estonia were already participating in the project, except those that are populated mainly by Russians who speak little or no Estonian. For these areas, the consent form, health-data questionnaire and all information material had to be translated into Russian. Although this was mostly complete by September, the EGP was still translating the education materials used in training nurses and physicians—every health professional participating in the EGP has to undergo a four-day training course.

Even more important than the technical and logistic setup of Eesti Geenivaramu, the Estonian gene bank, is its legal basis, the HGRA. The Gene Forum 2003 meeting was preceded by the 'From Ethics to Law' seminar, organized by the Estonian Genome Project Foundation and the Council of Europe, during which various speakers explained the rationales behind the HGRA and discussed many of the legal and commercial implications of the project. Indeed, the HGRA, which regulates how the gene bank collects, stores and uses the collected samples and data, is a pioneering work in itself; as Ants Nõmper, a lawyer at Raidla & Partners (Tallinn, Estonia), pointed out,

the Estonian parliament had to solve many of the legal and ethical problems for the first time. Some basic regulations already existed in the Convention on Human Rights and Biomedicine of the Council of Europe but those were too "broad and soft" to provide sufficient legal basis for the direct requirements of human genome research, Nõmper said. The HGRA was drafted by Estonian geneticists, lawyers, physicians, ethicists, data protectors and politicians, and was adopted with only minimal changes by the Estonian parliament. It maintains that the EGP operates as an independent organization and, although currently financed by the Estonian government, it is expected to create its own funds in the future by selling access to its databases.

"We tend to believe that the enemy of privacy is science. I think it's not a good concept."

One important issue was to solve the problem of who owns the data and tissues, in a way that allows researchers to use the information but also protects the rights of the individual, explained Tarmo Sild, a lawyer at HETA Law Offices in Tallinn, who was involved in drafting the HGRA. Their solution was to require participants to waive their ownership of tissue samples and health data and transfer it to Eesti Geenivaramu, which has the "right to possess, use and dispose" of it under the conditions defined by the HGRA. This might not necessarily be a solution for everyone—the legal basis for the Latvian genome database, for instance, allows individuals to retain ownership. Waiving ownership also means that participants in the EGP cannot simply withdraw their consent and demand that the samples and data be destroyed, although exceptions exist. Sild also explained that the HGRA distinguishes between three different levels of ownership: tissue, basic genetic data and "elaborate" genetic data from research. The first two are owned by Eesti Geenivaramu, whereas elaborate data created through scientific research are not regulated by the HGRA, which means that researchers and companies can claim patent protection of their findings. "In a way, [HGRA] functions as a bridge between the collection of material and patents," Sild commented.

Nömper further described the rationale of the HGRA to use “open consent” to allow researchers to perform experiments and data mining. “Population-based databases ... have raised several new questions that cannot be easily answered using the classical form of ‘informed consent’ [where all future use of the material has to be spelled out],” he explained. “Although ... the consent form used within the context of the EGP seems to be rather broad and unconditional, it is still as specific as possible without unduly limiting the scientific and healthcare value of the Estonian Gene Bank.” Another feature is the requirement for explicit consent, in which it differs from the Icelandic project, which uses ‘assumed consent’ with an opt-out model. Furthermore, the HGRA prohibits any form of negative or positive sanctions, such as free drugs or remuneration. However, Nömper pointed to public perception problems: “Some surveys have shown that a big proportion of potential gene donors are driven by incorrect imaginations, such as genetics will cure every disease and there will be new drugs available for free.”

The ‘From Ethics to Law’ seminar also discussed other aspects of population databases that go beyond the immediate impact of how to operate and regulate them, most notably the nagging question about privacy. During the 1990s, privacy was mainly a perceived problem for patients and families suffering from inheritable diseases, Tikk said, but “nowadays the problem is the privacy of whole populations.” And this still needs to be solved, said Judit Sándor, Associate Professor of Law at the Central European University in Budapest, Hungary. “The concept [of privacy] as we are using it now was mainly developed in American jurisprudence,” she said, but in general there is no common understanding of what it means. It is also complicated by an inherent dilemma, as democracies on the one hand are based on openness and on its citizens’ right to know, but on the other, they need to protect their citizens’ right of privacy as well. “It is a subject of very careful and very sensitive balancing between different interests,” Sándor said. Furthermore, it changes over time. “Technology was always the driving force to extend privacy,” she pointed out, noting that the invention of the telephone was the first

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case when privacy issues became important; biotechnology might be just the most recent one that has created the concept of ‘genetic privacy’. And it has added another potential dilemma, namely to protect the individual’s right of privacy versus the right of the researchers to perform their work. “We tend to believe that the enemy of privacy is science,” Sándor commented. “I think it’s not a good concept.” Andres Metspalu, Professor of Biotechnology at the University of Tartu and the father of the Estonian Genome Project, asserted in conversation that currently there might be too much emphasis on the individuals’ right of privacy, which disregards families’ and society’s rights when it comes to inherited diseases. But that might change with further advances in biotechnology and the implementation of population DNA databases, he thinks, and these problems will be eventually replaced by other issues 10–20 years from now.

Whereas the ethics seminar provided an overview on the legal and ethical implications of genome and health databanks, the Gene Forum conference highlighted the huge interest in using population databases for medical care and research. Various speakers explored the new possibilities of population genetics, from using pharmacogenomics to make more efficient use of existing drugs and to circumvent side effects, to finding new drug targets for a wide range of ailments and diseases. But the ultimate goal—to use health and DNA databases for predictive medicine—is still at the concept stage and will require major investments in biomedical research and information technology to solve the various logistical challenges. Nevertheless, the idea of personalized medicine based on population DNA and health databases is catching on. Latvia and Norway are also planning to establish their own population databases. In the UK, the MRC and the UK Department of Health plan to start the UK Biobank project to collect samples and health data from up to 500,000 volunteers between 45 and 70 years old. By following up on

the health of these volunteers, Biobank will provide the raw data with which researchers can measure the effect of genetic, environmental and lifestyle factors on health risk, “providing clean food for the R&D machinery,” as Biobank’s Norton put it. Although rather limited in size compared with the EGP, he sees it as a first step for the UK. “We won’t necessarily have the final answer but we think that Biobank will move the research ahead,” he said.

“The problem is the misunderstanding in the public about what genetics can do and what it cannot do.”

However, population DNA and health databases cannot be established without the participation of the public, who first need to be convinced. “It is essential that we have trust and respect from the public,” Norton said, “otherwise we are extremely vulnerable.” And that calls on the scientists to follow good practice guidelines to prevent backlash from both the public and the economic sector, as Leslie Platt Jr, a principal at Ernst & Young LLP (McLean, VA, USA) and leader of its Health Sciences Research Compliance Group, told the participants of the meeting. “It is very important in the new global economy ... that we do this properly. It is important that we do this responsibly.” And there is a lot of convincing to do. Whereas surveys showed that up to 80% of Icelanders support their project, the situation in Estonia is not yet as positive. In a 2003 poll, 40% of Estonians said they support the project, up from 32% in 2002. Only 2% were against it, but another 30% said that they would wait for the project to develop before they participated. Also interesting is that about 19% thought that they needed more information. Clearly, what is needed is the education of society at all levels on the challenges and benefits of genome and health databases and on their role in personalized medicine. This means more education about genetics and biology as well. As Metspalu put it, “The problem is the misunderstanding in the public about what genetics can do and what it cannot do.”

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