Ethical and Policy Issues in Biobanks

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“This project is designed to study the expression of coronary artery disease in a normal or unselected population and to determine the factors predisposing to the development of the disease through clinical and laboratory examination and long term follow-up of such a group.”

- Gilcin Meadors, 1947
  Framingham Project Director
<table>
<thead>
<tr>
<th>Study</th>
<th>Start Year</th>
<th># Participants</th>
<th>Sponsor</th>
<th>Samples/DNA</th>
<th>Health Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham</td>
<td>1947</td>
<td>14,428</td>
<td>NHLBI/NIH</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>NHANES: I,II,III,IV</td>
<td>1971</td>
<td>5,000 /yr</td>
<td>CDC, DHHS</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Nurses’ Health Study</td>
<td>1976</td>
<td>122,000</td>
<td>NINR/NIH</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>The Nun Study</td>
<td>1986</td>
<td>678</td>
<td>NIA/NIH, Kleberg Foundation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Multiethnic Cohort Study</td>
<td>1993</td>
<td>215,000+</td>
<td>NCI</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Jackson Heart Study</td>
<td>2000</td>
<td>6,500</td>
<td>NHLBI, (NCMHD)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>NUGene</td>
<td>2002</td>
<td>6,422</td>
<td>Northwestern</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Marshfield Clinic</td>
<td>2002</td>
<td>40,000</td>
<td>Marshfield Medical Clinic Res. Foundation</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Hispanic Community Health Study</td>
<td>2006</td>
<td>16,000</td>
<td>NHLBI</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Children’s Hospital of Philadelphia</td>
<td>2006</td>
<td>100,000</td>
<td>JR Stokes RI</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
Benefits from Past Research Using HBM

• Cancer
  – Studies of precancerous lesions of cervix lead to Pap smears
• Infectious disease
  – Stored samples helped researchers sequence the SARS virus
  – Understanding pandemic influenza
• Medical Devices
  – Artificial joints developed with research on stored blood, bone
  – Pacemakers developed with research on cardiac tissue
More Stuff Than Ever

Table 2-1. Stored Human Biological Materials in the United States

<table>
<thead>
<tr>
<th>Type of Repository</th>
<th>Number of Cases*</th>
<th>Number of Specimens**</th>
<th>New Cases/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large Tissue Banks, Repositories, and Core Facilities</td>
<td>&gt;2,600,000</td>
<td>&gt;96,000,000</td>
<td>364,825</td>
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<tr>
<td>Longitudinal Studies</td>
<td>&gt;263,500</td>
<td>&gt;263,500</td>
<td>unknown</td>
</tr>
<tr>
<td>Pathology Specimens</td>
<td>&gt;160,000,000</td>
<td>&gt;160,000,000</td>
<td>&gt;8,000,000</td>
</tr>
<tr>
<td>Newborn Screening Laboratories</td>
<td>&gt;13,500,000</td>
<td>&gt;13,500,000</td>
<td>&lt;10,000 to &gt;50,000</td>
</tr>
<tr>
<td>Forensic DNA Banks</td>
<td>380,000</td>
<td>380,000</td>
<td>unknown</td>
</tr>
<tr>
<td>Umbilical Cord Blood Banks</td>
<td>18,300</td>
<td>18,300</td>
<td>unknown</td>
</tr>
<tr>
<td>Organ Banks</td>
<td>unknown</td>
<td>&gt;75,500</td>
<td>&gt;75,500</td>
</tr>
<tr>
<td>Blood Banks</td>
<td>unknown</td>
<td>~12,000,000</td>
<td>~12,000,000</td>
</tr>
<tr>
<td>Total</td>
<td>&gt;&gt;176,500,000</td>
<td>&gt;&gt;282,000,000</td>
<td>&gt;20,000,000</td>
</tr>
</tbody>
</table>


Excludes:
- Proprietary banks
- Classified banks
- Military
In More Places Than Ever
The Accelerant Effect of the Genome Project: Personalized Medicine

If it were not for the great variability among individuals, medicine might as well be a science and not an art.

— Sir William Osler (1892)
Creating incentives for genomic research to improve targeting of therapies

Barbara J Evans¹,², David A Flockhart¹,³ & Eric M Meslin¹,⁴,⁵

Pharmacogenomics is the study of genetic variability in the way people respond to medicines, traced to the expression of genes related to disease susceptibility and drug response at the cellular, tissue, individual and population levels¹,². It has potential to improve targeting of therapies through tests to identify, in advance, individuals who are genetically disposed to respond favorably or unfavorably to particular medicines³. Recent successes included demonstration of a genetic strategy to identify lung cancer patients most likely to benefit from treatment with gefitinib (Iressa), a drug previously recognized as ineffective in most cancer patients⁴,⁵.

Government-funded research had a critical role in determining the target population that benefits from gefitinib. This highlights a question that looms over pharmacogenomics: do private-sector companies have adequate commercial incentives to pursue research aimed at improving the targeting of therapies? If not, then is governmental intervention required and in what form?

Incentives for pharmacogenomic research

Attractive reasons exist for private companies to conduct pharmacogenomic research, but there are some lingering incentive problems that may limit the extent to which these incentives are realized. There is the prospect that targeted therapies, although sold to smaller patient subpopulations, may command premium prices based on superior reliability⁶, as has been seen with trastuzumab (Herceptin). Products tailored to subpopulations that need treatment but are not currently served could generate new sources of revenue. There has been a recent trend among regulatory authorities worldwide to require clearer indication of patients who are likely to benefit from new treatments⁷. This tends to encourage pharmacogenonomic research, as do regulatory requirements to show improved efficacy and cost effectiveness of drugs⁸. Problems with safety and efficacy are major reasons for costly product failures late in clinical trials⁹ or after drugs reach market, as recently occurred with rofecoxib (Vioxx). This makes it attractive to explore genomic strategies that offer new tools to predict safety and efficacy¹⁰. Yet many of these benefits are speculative and long term. Are they enough to overcome concerns that targeted therapies may disrupt a long-profitable business model and erode market share?

Worldwide, there is a sizeable lawful trade in drugs that do not work for the individuals to whom they are prescribed. On average, it is believed that only 60% of prescriptions written will be effective in 65–85% of the people who take them to treat high blood pressure⁶. Cancer therapies approved by the US Food and Drug Administration may help as few as 5–15% of patients, depending on the cancer, and then add only months, not years, to their lives¹³. Treatments fail for many reasons, not all linked to genetics. Still, pharmacogenomic research has the potential to eliminate billions of dollars of true waste—spending that does not help patients—freeing funds for other critical uses. Even if the health care industry as a whole would reap benefits, there may be individual winners and losers, and prospective losers may resist. Companies with high levels of sales to nonresponding individuals seemingly have the most to lose. Commercial incentives for research may be weakest precisely where improved targeting is most needed.

This problem flows from a special set of legal, ethical and commercial rules that apply to health care and differ sharply from the rules under which most other industries operate. If new refrigerators hurt 7% of customers and failed to work for another one-third of them, customers would expect refunds. In many states, manufacturers would be strictly liable for the injuries, and there would be implied warranties even if the
“Please pay attention, as the ethics have changed.”
Exhibit 2-C: Iceland’s Health Records Database

A plan to construct a central database of health records in Iceland has garnered recent international attention both for its promise for human genetics research and for the ethical questions that it raises. The database, which will contain "nonpersonally identifiable health data" from the medical records of Icelandic citizens, was authorized by recent legislation passed in Iceland’s Parliament (Act 1998). Like collections of human biological materials stored in the United States, the centralized bank of health records is regarded as a potentially valuable research resource. It also raises familiar ethical questions, including "What constitutes personally identifiable information?" "How can privacy be protected in the course of research?" and "How should research involving patient data be conducted in an ethically acceptable manner?" (Act 1998).*

The information to be included in this central database will come from a variety of sources, including health records, genealogical records, and genetic information from biological samples collected with informed consent from volunteers. The new legislation grants Decode Genetics a 12-year license to construct, operate, and receive a substantial share of the profit from the database. During that time, Decode will use the vast amounts of patient information to conduct research into the origin and nature of various diseases (Lyall 1999).

Several factors make Iceland a unique location for genetics research and its health records database a particularly valuable tool for researchers. First, Iceland’s relatively homogeneous gene pool facilitates research into disease-causing mutations. In addition, Iceland’s state-financed health care system maintains thorough health records, and various public and private sources maintain extensive genealogical records. When these records are combined with the data from biological samples, the database becomes a valuable tool in tracing the genetic factors of various diseases (Enserink 1998; Spector 1999). As an official of Iceland’s Ministry of Health and Social Security comments, "This situation imposes on us an ethical obligation and gives us a unique opportunity to promote medical sciences" (Haraldsdottir 1999a).

However, some observers believe that this database raises serious ethical questions. Discussion has centered on three issues: consent, privacy, and the commercialization of the database (Enserink 1999; Lewontin 1999; Lyall 1999). First, Iceland’s new law allows information to be submitted without patient consent. All that is required is the consent of the health institutions that hold the medical records. Patients may "opt out" of participation by informing the Director General of Public Health of their wishes. Some have questioned whether this plan is appropriate in light of the potentially sensitive nature of the information (Lewontin 1999; Lyall 1999; Schwartz 1999). Approximately 10 percent of citizens are estimated to have opted out or plan to opt out of participation in the database.

Privacy is another concern. The very factors that make the database scientifically useful also might create a situation in which personal identification can be deduced from "nonpersonally identifiable data." For example, the new legislation permits Decode to process data on the health database and connect it with genealogical and "genetic data" (Act 1998). Although the law stipulates that linking databases is allowed "provided that data are processed and connected in such a way that they cannot be linked to identifiable individuals," some experts have questioned how such requirements will work in practice (Act 1998). At least one privacy expert who evaluated the database says that identification would be easy to deduce (Berger 1999; Schwartz 1999). Still, it is difficult to know how to weigh the impact of such invasions of privacy in a country with a national system of medical insurance and in which most genealogical data is exempt from basic privacy laws (Spector 1999).

Finally, observers have questioned whether the plan to allow one company to own and operate the database is in the best interests of either science or of the people of Iceland. Although the law permits Iceland’s Ministry of Health free access to the database, it permits access by others only so long as such access does not affect Decode’s commercial interests. It remains unclear what the scope of access to the data will be in practice (Haraldsdottir 1999a).
Informed Consent

- Consent for specific one-time use
- Consent for non-specific future use
- Stewardship models
- Broad, Targeted
- Opt-in, Opt-Out

Development of a Large-Scale De-Identified DNA Biobank to Enable Personalized Medicine

DM Roden1,3, JM Pulley4, MA Basford4, GR Bernard2,4, EW Clayton5,6, JR Balser3,4 and DR Masys7

Our objective was to develop a DNA biobank linked to phenotypic data derived from an electronic medical record (EMR) system. An "opt-out" model was implemented after significant review and revision. The plan included (i) development and maintenance of a de-identified mirror image of the EMR, namely, the "synthetic derivative" (SD) and (ii) DNA extracted from discarded blood samples and linked to the SD. Surveys of patients indicated general acceptance of the concept, with only a minority (~5%) opposing it. As a result, mechanisms to facilitate opt-out included publicity and revision of a standard "consent to treatment" form. Algorithms for sample handling and procedures for de-identification were developed and validated in order to ensure acceptable error rates (<0.3 and <0.1%, respectively). The rate of sample accrual is 700–900 samples/week. The advantages of this approach are the rate of sample acquisition and the diversity of phenotypes based on EMRs.
The relationship between SNPs needed for good research and protection of privacy

Source: Altman, (2005)
Commercialization

- The Moore objection
- Commodification as a moral wrong
- Sources of sponsorship
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Fighting back: deCODE's Kari Stefánsson says Iceland's Data Protection Authority has reversed its position.

It's difficult to define. 

Other geneticists, such as Daniel MacArthur of Massachusetts General Hospital in Boston, suggest that although deCODE does not seem to have violated the privacy of individuals, from an ethics standpoint its researchers should at least attempt to obtain informed consent.

It's divided on how big a blow DPA's decision will be. 

In these studies, numbers are always a big advantage. But I don't think it's a deal breaker for their research.
Public Willingness to Participate in Biobanks and Share Health Information
Participation in Biobanks

**Indiana University Cancer Patients**
- ~85% agreed that stored tissue could be used in unspecified future research
- 60-70% would not require re-contact each time tissues were used

**Women and Pregnant Mothers**
- 77% felt predictive health research was worthwhile
- Most supported consent for future use
  - Haas, Renbarger, Meslin, Drabiak, Flockhart (2008)

**Parental Attitudes—Pediatric Biobanking**
- 68% agree/strongly agree pts should have chance to be in research
- 81% somewhat/very likely to permit child’s blood to be donated to biobank
- 91% have fair/great deal of trust in hospitals to protect confidentiality
- 62% oppose/strongly oppose commercialization
  - Harland, Miller, Meslin, Wolf, Denne (2010)

**Physicians and Nurses—Pediatric Biobanking**
- MD and RN attitudes toward pediatric biobanks are similar
- Broad support for a pediatric biobank from HCP, including support for unspecified use of samples
Patient Control Over Health Info in EMR

- No patients willing to share all EMR information (EMR) with all potential recipients.
- Patients with and without sensitive records preferred less sharing of sensitive versus less-sensitive information.
- Patients want granular privacy control over health information in electronic medical records

Caine & Hanania, J Am Med Inform Assoc 2013
“When people in the general community were asked if they approved of their information being used in this way, they were found to be not only supportive of it, but they questioned why it was not already being done.”

Source: Stanley and Meslin (2007)
"Soccer is the sport of the future in America ... and it always will be." This oft-used epithet poking fun at the promise of the "beautiful game" in the United States can seem uncomfortably apt when applied to genomic medicine. It's now been 10 years since humans deciphered the digital code that defines us as a species. Although it may be hard to overestimate the significance of that achievement, it is easy to misconstrue its meaning and promise. People argue about whether mapping the human genome was worth the investment (1–3). With global funding for genomics approaching $3 billion/year (4), some wonder what became of all the genomic medicine we were promised (5). It thus seems an appropriate time to take stock of whence the real benefits from genomic research may come and how best to attain a future in which genomics improves human health.

Recent methodological progress in genomics has been breathtaking. We now understand that substantial impediments to realizing many of the claims most people made for genomics are largely due to the relatively low relative risks (i.e., compared with the much more meaningful absolute risks) of many of the most common diseases and rare genetic diseases. The difficulty of changing behaviors. The idea that genetic information will promote a healthy lifestyle has emerged as a dominant claim by those who promote genomic medicine (16, 17). However, there is little evidence that simply telling someone they are at a genetically increased risk for heart disease or diabetes, for example, leads to lasting beneficial changes in diet or exercise habits (18, 19).

The paradox of risk information. Even if, despite evidence to the contrary, knowledge of one's genetic status...
African genomics project takes shape at Cape Town meeting

CAPE TOWN — More than 200 medical researchers met under sunny skies here on 4 and 5 March to discuss practical ways for the African continent to start benefiting from advances in genomics.

The meeting was to inform the design of the £60 million, five-year Human Heredity and Health in Africa (H3Africa) initiative. The initiative, funded by the Wellcome Trust, a UK medical research charity, and the US National Institutes of Health (NIH), aims to bring modern medical technologies to bear on Africa’s deadly disease burden.

Africans are extremely genetically diverse—yet little is known about this variance and its health impact. Today, three quarters of the thousands of genetics studies completed worldwide have been conducted on populations of European ancestry. Africans are also poorly represented in international genetics projects such as the 1000 Genomes and 1000 Genomes projects.

This gap presents both an opportunity and a challenge for Africa, NIH director Francis Collins said at the meeting. The rapidly falling cost of sequencing and genetic analysis has put the technology within reach for sub-Saharan Africa researchers. Moreover, the importance of Africa as the birthplace of humanity makes African genetics an important and inspiring area of study, he said.

But the continent’s poor health systems—including some medical data, low research capacity and a lack of trained health professionals—hinders this research effort being managed outside the continent, he continued. “We need capacity building to cross these other barriers,” he said.

The H3Africa initiative plans to help plug African genomics knowledge gap by addressing shortages in infrastructure, training and regulations. Although the exact goal for H3Africa remains flexible, a white paper presented at the Cape Town meeting outlined a number of possible activities to initiate. These include developing regional centers of excellence in genomics and sequencing and a continent-wide information network.

Grading reactions

Researchers said that reactions to current used drugs vary greatly between Africans and non-Africans. For instance, the presence of a duplication within CYP2D6, a gene associated with adverse reactions to common antidepressants, varies widely between African populations, from being totally absent among South Africa’s Xhosa population to being present in 46% of Ethiopians and nearly 50% of Algerians.

Other studies have shown that small differences in drug metabolism can lead to significant differences in treatment outcomes. For example, in the case of abacavir, people from African populations have a higher incidence of adverse reactions.

Others have pointed out that similar genetic changes that underlie disease susceptibility can be found in different populations. For instance, a recent study found that people of African ancestry are more likely to suffer from sickle cell disease.

While researchers talk to people in Europe, they don’t talk to each other, “Charles Rotimi said at the meeting,” said Rotimi, who is director of the NIH’s Office of Biomedical Research.”

The aim of the meeting was to change this. The meeting concluded with a call to action on the part of all of the attendees to participate in future meetings and to share their data with others. The meeting was well attended by participants from all over the world, and the organizers hope that this will continue in future meetings.”

Complex Patterns of Genomic Admixture within Southern Africa

Desiree C. Petersen, Ondrej Libiger, Elizabeth A. Tindall, Rae-Anne Hardie, Linda I. Hannick, Richard H. Glashoff, Mitali Mukerji, Indian Genome Variation Consortium, Pedro Fernandez, Wilfrid Haacke, Nicholas J. Schork, Vanessa M. Hayes

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In: ethnic and applied research in health information