Ethical, Legal, and Social Issues in Genomics: Reflecting Back, Planning Ahead

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Reflecting Back

The Ethical, Legal, and Social Implications (ELSI) Program in the Division of Extramural Research at the NHGRI*

- Established in 1990
- Function and purpose (multidisciplinary focus):
  - Identify and examine key ethical, legal, and social issues
  - Stimulate public discussion
  - Develop policy options
  - Expand public education
Areas of Research

• Privacy and Fair Use
  – Privacy and confidentiality, Genetic discrimination
• Clinical Integration
  – Impact of genetic testing
• Genetic Research
  – Research design; Informed consent
• Education and Resources
  – ELSI and genetics-based curriculum
What ELSI is New?

On Monday the Genomics Law Report will debut a series of guest commentaries by industry, academic and thought leaders in the fields of genomics and personalized medicine. The series is modeled on the Nature Genetics 2007 Question of the Year (“What would you do if it became possible to sequence the equivalent of a full human genome for only $1,000?”) with a slight modification.

Entitled What ELSI is New?, the series was motivated by the following question: “What do you believe is the most pressing ethical, legal and social issue (ELSI) that must be addressed by the fields of genomics and personalized medicine? The series is intended to help frame the promise of genomics and personalized medicine.

As the series gets under way we encourage you to share your own views on what the most pressing ethical, legal and social issues in science are.
Planning Ahead

Psychosocial and Ethical Issues in Genomics Research

Psychosocial and Ethical Issues in Genomic Medicine

Legal and Public Policy Issues

Broader Societal Issues

Green ED, Guyer MS, NHGRI, Charting a course for genomic medicine from base pairs to bedside, Nature 470: 204-13 (2011)
Planning for the Future of ELSI

NHGRI ELSI Assessment Panel (EAP) Report (May 2008); Green ED, Guyer MS, NHGRI, Charting a course for genomic medicine from base pairs to bedside, Nature 470: 204-13 (2011)
The complete genome of an individual by massively parallel DNA sequencing


Box 1

Protection of human subjects
Is institutional review board approval required for this project?
Considerations. Approval by an institutional review board (IRB) is required for all research involving human subjects. Federal regulation defines research as a 'systematic investigation, including research, development, testing and evaluation, designed to develop or contribute to generalizable knowledge.' A human subject is defined according to the regulations as 'a living individual about whom an investigator ... conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.' (45 CFR 46.102). Baylor College of Medicine, Houston, Texas, requires that all proposed activities at the college be reviewed to determine if they meet the regulatory definitions for research involving human subjects. IRB reviews help to ensure ethical research conduct and appropriate subject protection. It also sets an important standard for future research in the field of personalized genomics.

Management. The research protocol was written in consultation with an ethicist and reviewed by the Baylor College of Medicine IRB. The research participant’s identity was not revealed to the IRB to ensure objectivity. Although the practical management of many of the ethical issues depended on the unique expertise of the research participant, this did not affect review or approval of the research protocol.

Returning research results to research participants
Should the research participant be able to receive information about their individual genome sequence?
Considerations. Dr Watson requested that he receive information about all data generated from this research project. Generally, patients have a right to receive medical information, but the right does not extend to genetic information. Because Dr Watson is knowledgeable about and familiar with the current literature in genetics, he was informed about what a patient needs to know and what he should not. Research subjects have the right to know about potential research subjects.

Data release and data flow
Should the participant’s genome sequence be publicly released?
Considerations. There is great scientific interest in accessing and studying the data generated from this project. To maximize scientific and clinical use, public data release is strongly encouraged in genomic research. Dr Watson is personally committed to a policy of open access to DNA data. However, because DNA is a unique identifier, there are privacy risks associated with data sharing. Because this project was publicly announced and Dr Watson was individually identified, there was concern about his privacy interests and the potential harm that could result from the misuse of his genetic information.

Management. An individual can waive their right to privacy and share personal information with others. Dr Watson decided to share his personal genome by releasing it into a publicly accessible scientific database. The privacy risks associated with public data release were explained.

What if any, obligations are owed to third-party relatives?
Considerations. Because genetic information is familial by nature, Dr
Research ethics and the challenge of whole-genome sequencing

Amy L. McGuire, Timothy Caulfield and Mildred K. Cho

Abstract | The recent completion of the first two individual whole-genome sequences is a research milestone. As personal genome research advances, investigators and international research bodies must ensure ethical research conduct. We identify three major ethical considerations that have been implicated in whole-genome research: the return of research results to participants; the obligations, if any, that are owed to participants’ relatives; and the future use of samples and data taken for whole-genome sequencing. Although the issues are not new, we discuss their implications for personal genomics and provide recommendations for appropriate management in the context of research involving individual whole-genome sequencing.

We propose specific recommendations for each of these ethically controversial issues, which can be used to guide research practice and stimulate policy development (Box 1).

Reporting back research results

When James Watson received a miniature hard drive containing his personal genome sequence, it was more than a mere symbolic gesture. Although Watson is a scientist with an individual and academic connection to the personal genome initiative, at that moment he was also a research participant receiving the raw data from a unique genetic research project.

Much has been written on when and how research participants should receive genetic research results.5-8 Knoppers and colleagues suggest that the scope of the duty to disclose will vary depending on “the type of study, the clinical significance and reliability of the information, and whether

On 31 May 2007, James Watson was handed a miniature hard drive containing his personal genome sequence, which was subsequently uploaded to publicly accessible databases. Craig Venter’s personal genome was published a few months later (7). These projects represent research milestones. They also present an opportunity to examine the ethical, social, and clinical implications of personal genomics.

Excitement over these projects has been tremendous. Many are willing to pay a hefty price to see. Scientists predict that within 5 years DNA sequencing technologies will be affordable enough that personal genomics will be integrated into routine clinical care (2). Companies are responding by offering their services for ancestry tracing, forensics, nutritional advice, reproductive assistance, and even social networking. It will not be long before companies are able to offer a “Facebook-like service centered around our genomes” (3). The medical community needs to consider the ways in which routine generation of this information will affect our health system.

The Future of Personal Genomics

Amy L. McGuire, Mildred K. Cho, Sean E. McGuire, Timothy Caulfield

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Reference and Notes
Invention Of the Year

Your genome used to be a closed book. Now a simple, affordable test can shed new light on everything from your intelligence to your biggest health risks. Say hello to your DNA—if you dare.

BY ANITA HAMILTON

The Retail DNA Test
Direct-to-Consumer Genetic Testing: Is It the Practice of Medicine?

Cynthia Marietta and Amy L. McGuire

Understanding of the human genome and its functional significance has increased exponentially since the completion of the Human Genome Project (HGP) in 2003. The HGP fueled the discovery of more than 1,800 disease genes and paved the way for researchers to identify and test for genes suspected of causing inherited diseases. Currently, there are more than 1000 genetic tests for human diseases and conditions on the market. These tests can play an integral role in the delivery of health care by providing information that could potentially form the basis for profound life decisions, such as whether to undergo a prophylactic mastectomy, whether to terminate a pregnancy, or whether to take a particular drug or diseases, traits, and conditions by genotyping thousands of gene loci in each individual. The variety of genetic information tested for complicates the issue of whether these companies are providing information for recreational purposes only or whether they are also providing medical diagnostic information. The pertinent legal issue relates to whether the services offered by DTC genetic testing companies fall within the scope of medical practice, and if so, to what extent must a physician or other health care provider be involved?

Types of DTC Genetic Testing Services Available

Currently, there are approximately 35 DTC genetic testing companies doing business in the United States.
Online survey: Facebook.com users (2008)

- Demographics (n=1087)
  - Age: 35 (12)
  - Race: 83% Caucasian
  - Gender: 73% Female
  - Education: 60% College Grad

![Pie chart showing usage preferences]

![Bar chart showing reasons for use]

- General curiosity
- See if specific disease runs in family or is genetic
- Learn about genetic make-up without going through doctor
2011 study of 2037 Navigenics consumers: 26.5% reported sharing results with their physicians

Bloss et al., NEJM 2011
An Unwelcome Side Effect of Direct-to-Consumer Personal Genome Testing
Raiding the Medical Commons

Amy L. McGuire, JD, PhD
Wylie Burke, MD, PhD

It is now possible for individuals to learn about their genetic susceptibility to dozens of common and complex disorders, such as coronary artery disease, diabetes, obesity, prostate cancer, and Alzheimer disease, without ever seeing a physician. Direct-to-consumer personal genome testing companies hope to empower consumers to take control of their health by providing tailored assessments of genetic risk based on reported associations between genomic variation and susceptibility to disease.

Several states limit or forbid this practice as a violation of patients' rights. Physicians are also accustomed to talking with patients about health information disclosed on the Internet or through other media outlets. At the same time, primary care physicians have limited time with patients, face many competing demands, and are poorly reimbursed for time spent counseling patients about preventive care. Patient concerns about direct-to-consumer test results have the potential to exacerbate these problems and strain already limited health care resources.

Raiding the Medical Commons

The clinical value, if any, of most direct-to-consumer personal genome tests remains unproven. A statistically significant association between a particular genomic variant and a disease does not necessarily mean that the presence of the variant causes disease. For example, a 2003 genome scan of nearly 1,000 people with Alzheimer disease detected a genetic variant in a protein called apolipoprotein E. The variant was not a cause of disease, however, but a risk factor for disease. As an example, the common variant of the apolipoprotein E gene that is associated with Alzheimer disease is found in 12% to 16% of the general population, but in 40% to 65% of people with Alzheimer disease. Such findings have led to studies of whether Alzheimer disease could be prevented or delayed by drugs that prevent the formation of plaques in the brain. The most useful test results will be those that provide meaningful information that can lead to treatment options.

The U.S. Federal Regulation

Labs that perform clinical testing services in the United States—such as diagnostic or genetic testing—are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (1). The CLIA regulates the quality of lab testing services, for example, by ensuring that laboratories are properly staffed and follow proper procedures. The genetic test kits that laboratories purchase from medical device manufacturers receive additional regulation by the U.S. Food and Drug Administration (FDA) as in vitro diagnostic devices (5). However, if a lab develops a test in-house (lab-developed test [LDT]), as opposed to purchasing the test from a device manufacturer, the test may escape FDA oversight. A lab cannot sell its LDTs for use by other laboratories but can use them to provide testing services to the public. Many LDTs arguably fall within the clearance process. The 510(k) clearance process does not necessarily require clinical trials but does require preemptive research to support the device’s risk classification and to validate any analytical or clinical claims that the sponsor plans to make about the device. Either way, some data-driven external regulatory review is required before a test can be sold for commercial use.

Regulating DTC Tests

DTC genetic tests may escape premarket review by FDA under a business model in which consumers send their samples to a CLIA-certified lab that performs testing using its own LDTs. In response to this concern, FDA recently sent letters to multiple companies involved in DTC testing (12), signaling its intent to assert jurisdiction over these tests.

No one regulatory strategy will be ideal for all DTC tests.
Expansion

ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS
Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS)

Notice Number: NOT-OD-07-088

Key Dates
Release Date: August 28, 2007
Effective Date: January 25, 2008

Other Relevant Notices
- October 20, 2006 (NOT-OD-07-013) - NIH Town Hall Meeting on the Proposed Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS).
- October 20, 2006 (NOT-OD-07-012) - Extended Comment Period for the Proposed Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS).
- August 30, 2006 (NOT-OD-06-094) - Request for Information (RFI): Proposed Policy for Sharing of Data obtained in NIH supported or conducted Genome-Wide Association Studies (GWAS).

Issued by
National Institutes of Health (NIH) (http://www.nih.gov)
Because individuals vary in their privacy-utility judgments “we recommend a stratified consent process in which all subjects who participate in future genomic sequencing studies are fully informed about how their DNA data may be broadcast and have the authority to decide with whom they want their data shared.”
Policy Concerns

• Giving participants information and control will decrease enrollment in genome research
• Giving participants options will result in only a select few ("information altruists") consenting to public data release

Randomized Trial of Consent for Data Sharing
R01 HG004333 (2007-2011)

Participants
Randomized with Waiver of Consent

- Traditional Consent
- Binary Consent
- Tiered Consent

Subjects debriefed, shown all three consents, and given the opportunity to change their consent form or data sharing option.

Interviewed
Planning for the Future of ELSI

Integration

Collaboration

Expansion

NHGRI ELSI Assessment Panel (EAP) Report (May 2008); Green ED, Guyer MS, NHGRI, Charting a course for genomic medicine from base pairs to bedside, Nature 470: 204-13 (2011)
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