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

Amy L. McGuire, JD, PhD
Center for Medical Ethics and Health Policy
Baylor College of Medicine

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

ELSI: Represents a new area of research

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News and analysis from the intersection of genomics, personalized medicine and the law

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What ELSI is New?

Posted by Dan Vorhaus on October 1, 2009

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 w
following question: *"What do you believe
issue (ELSI) that must be addressed by the fields of genomics and/
the series is to identify a wide range of ethical, legal and social issue
promise of genomics and personalized medicine.

As the series gets under way we encourage you to share your own

BOX 5

Genomics and society

Effectively examining the societal implications of genomic advances requires collaborations involving individuals with expertise in genomics and clinical medicine and experts in bioethics, psychology, sociology, anthropology, history, philosophy, law, economics, health services research and related disciplines.

Psychosocial and ethical issues in genomics research. These include ensuring appropriate protection of human research participants and addressing the perceptions of risks and benefits of participating in genomic studies; expanding the diversity of research cohorts; incorporating biological ancestry markers and self-identified race and ethnicity as variables in genomic studies; accomplishing effective community engagement; and including vulnerable populations (for example, children and the disabled) and deceased individuals in genomics research.

Psychosocial and ethical issues in genomic medicine. These include communicating with patients about the uncertainty and evolving nature of predictions based on genomic information; interpreting information from direct-to-consumer genetic tests; ensuring fair access to genomic medicine; assessing the effectiveness of genomically informed diagnostics and therapeutics; using genomic information to improve behaviour change interventions; addressing issues associated with pre-implantation, prenatal and postnatal genetic diagnoses; and determining how constructs of race and ethnicity relate to the biology of disease and the potential to advance genomic medicine.

Legal and public policy issues. These include intellectual property in genomics; insurance reimbursement for genomic services; regulation of genetic testing; regulatory and non-regulatory approaches for dealing with direct-to-consumer genetic testing; the regulation of pharmacogenomics and genomics-based therapeutics; protection against genetic discrimination and stigmatization; and uses of genomics in non-medical settings.

Broader societal issues. These include the implications of increasing genomic knowledge for conceptualizing health and disease; for understanding identity at the individual and group levels including race and ethnicity; for gaining insights about human origins and for considering genetic determinism, free will and individual responsibility.

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

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)

Integration:
Addressing Real Issues in Real Time

nature

LETTERS

The complete genome of an individual by massively parallel DNA sequencing

David A. Wheeler[1]*, Maithreyan Srinivasan[2]*, Michael Egholm[2]*, Yufeng Shen[1]*, Lei Chen[1], Amy McGuire[3], Wen He[2], Yi-Ju Chen[2], Vinod Makhijani[2], G. Thomas Roth[2], Xavier Gomes[2], Karrie Tartaro[2]†, Faheem Niazi[2], Cynthia L. Turcotte[2], Gerard P. Irzyk[2], James R. Lupski[4,5,6], Craig Chinault[4], Xing-zhi Song[1], Yue Liu[1], Ye Yuan[1], Lynne Nazareth[1], Xiang Qin[1], Donna M. Muzny[1], Marcel Margulies[2], George M. Weinstock[1,4], Richard A. Gibbs[1,4] & Jonathan M. Rothberg[2]†

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 (Baylor College of Medicine, IRB Procedures, November 2006). The research team and the Baylor College of Medicine IRB agreed that the activities associated with this project constitute research involving human subjects. IRB review helps 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 this right does not

Management. Because Dr Watson is knowledgeable about and familiar enough with the current literature in genetics to assess research findings and to make an informed decision about what risk information he does and does not want to receive, his right to redact information was respected. Decisions about redactions were made *a priori* and the problems associated with future findings, as well as general concerns about receiving specific genetic information, were discussed with a genetic counsellor. Dr Watson requested that all gene information about apolipoprotein E be redacted, citing concerns about the association that has been shown with Alzheimer's disease. These data were redacted and were not analysed by the research team. Again, this approach is not generalizable and may not be appropriate for other research participants.

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 broadcast were explained.

What, if any, obligations are owed to third-party relatives?

Considerations. Because genetic information is familial by nature, Dr

SCIENCE AND SOCIETY

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 with his entire 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[10–12]. 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

MEDICINE

The Future of Personal Genomics

Routine generation of whole-genome sequences will pose many health system challenges.

Amy L. McGuire,[1] Mildred K. Cho,[2] Sean E. McGuire,[3] Timothy Caulfield[4]

On 31 May 2007, James Watson was handed a miniature hard drive containing his personal genome sequence, which was subsequently uploaded onto publicly accessible databases. Craig Venter's personal genome was published a few months later (*1*). 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 be next. 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. Recent genomewide association studies that report an association between coronary heart disease and a common variant on chromosome 9, the actual risk of heart disease was only increased from 1% to 1.6% in homozygotes (*5*, *6*).

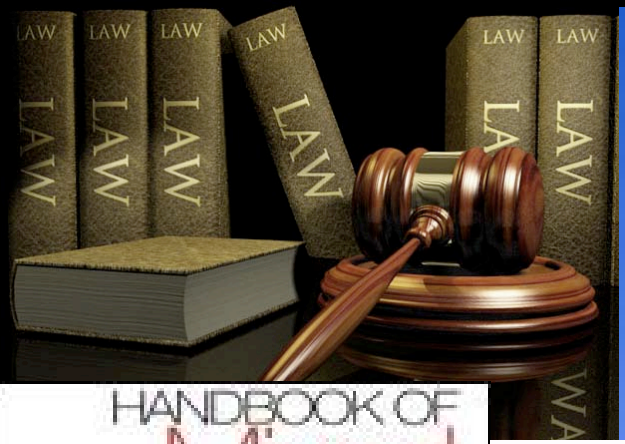
These studies are invaluable for understanding disease pathogenesis, but the present utility of this information for making treatment decisions is limited. Just because an association between genetic variation and disease is statistically significant does not mean that it is clinically meaningful (*7*). Moreover, simply knowing genetic risks and disease predispositions may not lead to better health decisions (*8*). For some, it might lead to fatalism and reduced compliance with healthy choices. As a result, many clinicians are "not at all enthusiastic about rushing out to test people in the clinic" for these genes (*7*). Although the scientific value of genomic research has been enormous, these emerging technologies have only had marginal impact on health care to date, at least at the population level (*9*).

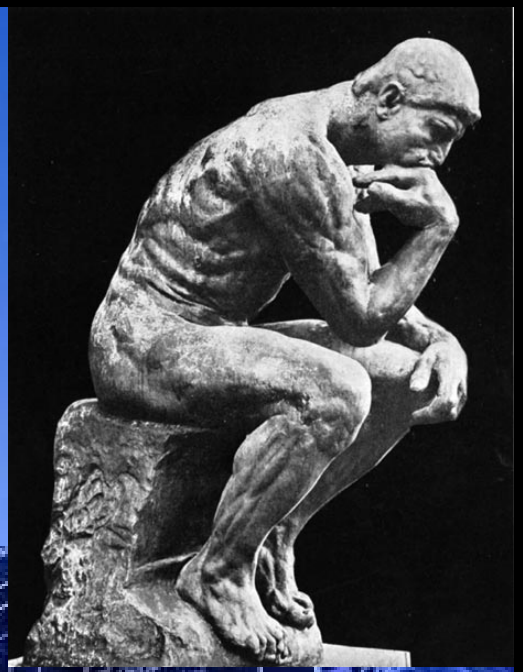
States) where there is limited access to basic health-care services for many. Should private health insurance companies and public health systems pay for DNA sequencing, genetic analysis, counseling, and follow-up clinical care? (*12*). Will physicians be reimbursed for the additional time spent educating patients about the significance of genetic risk information? Payers will likely decline coverage for genomic testing and counseling until it can be associated with improved patient outcomes and quality of care (*13*).

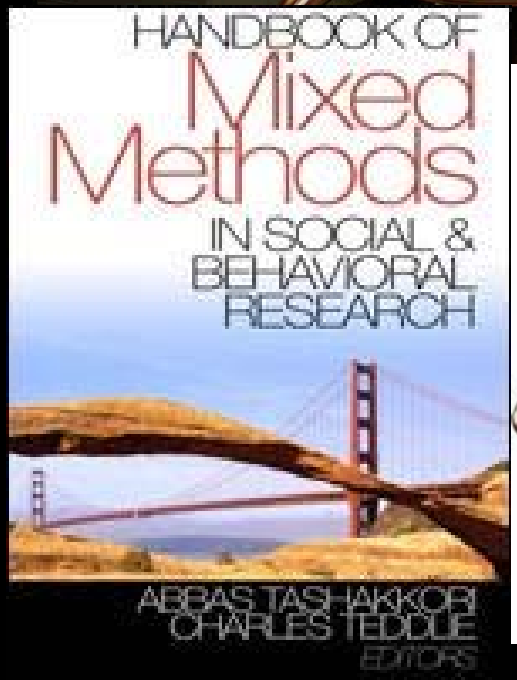
The potential clinical application of genomic information is great, as exemplified by the recent U.S. Food and Drug Administration approval of a label change for warfarin to include information on how genetic variations may affect drug response (*14*). However, successful integration of personal genomics into routine clinical care will require clear standards, multidisciplinary collaboration, and careful consideration of the ethical, social, and clinical implications.

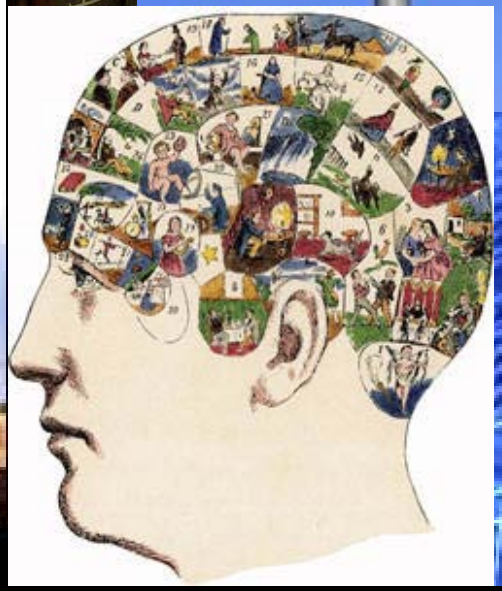
References and Notes

Collaboration
E+L+S









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

What Your Gene Test Can Tell You

Currents in Contemporary Ethics

Direct-to-Consumer Genetic Testing: Is It the Practice of Medicine?

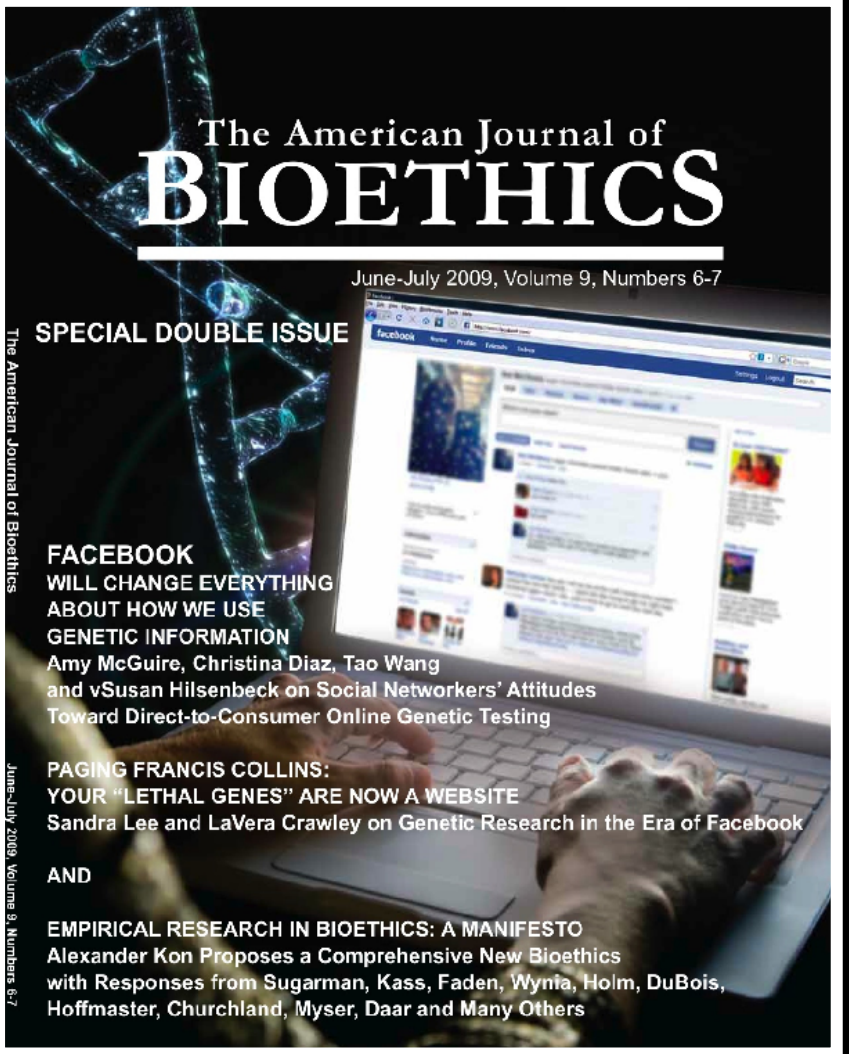
Cynthia Marietta and Amy L. McGuire

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.[1] 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

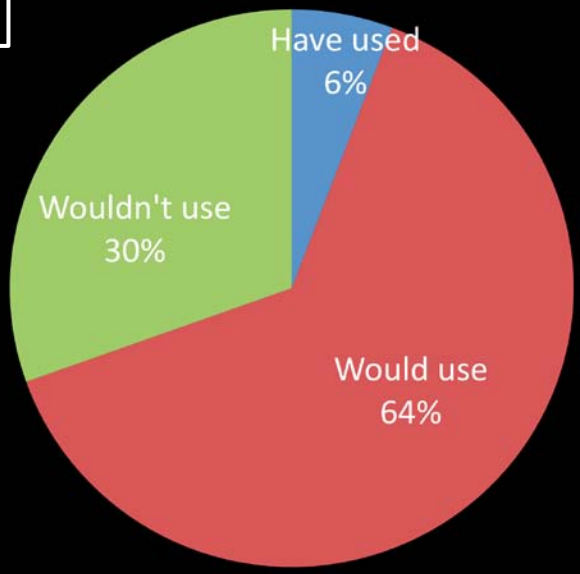


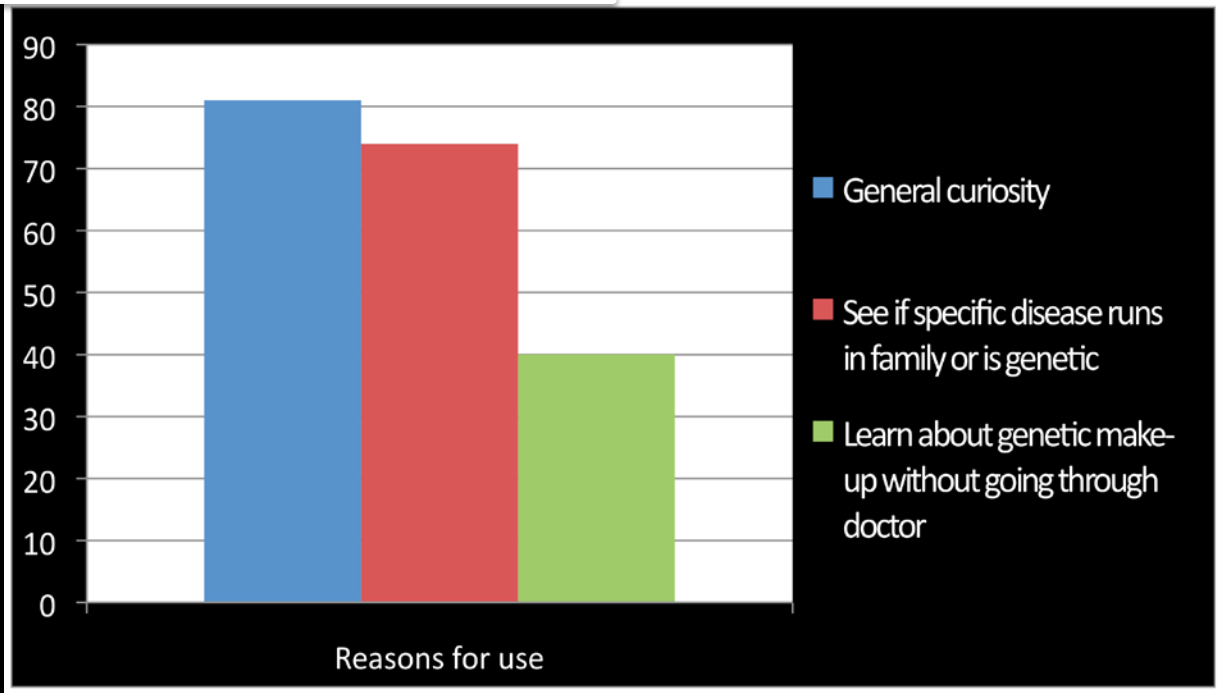
Law/Policy

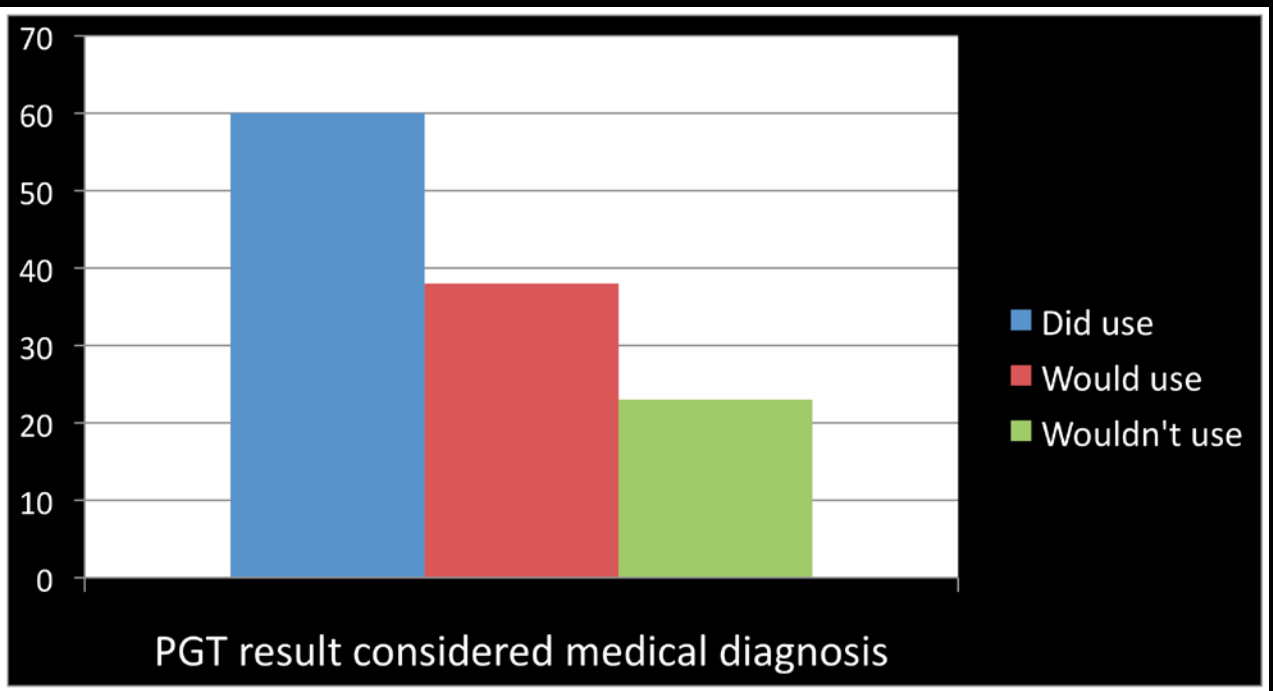
Social and Behavioral Research

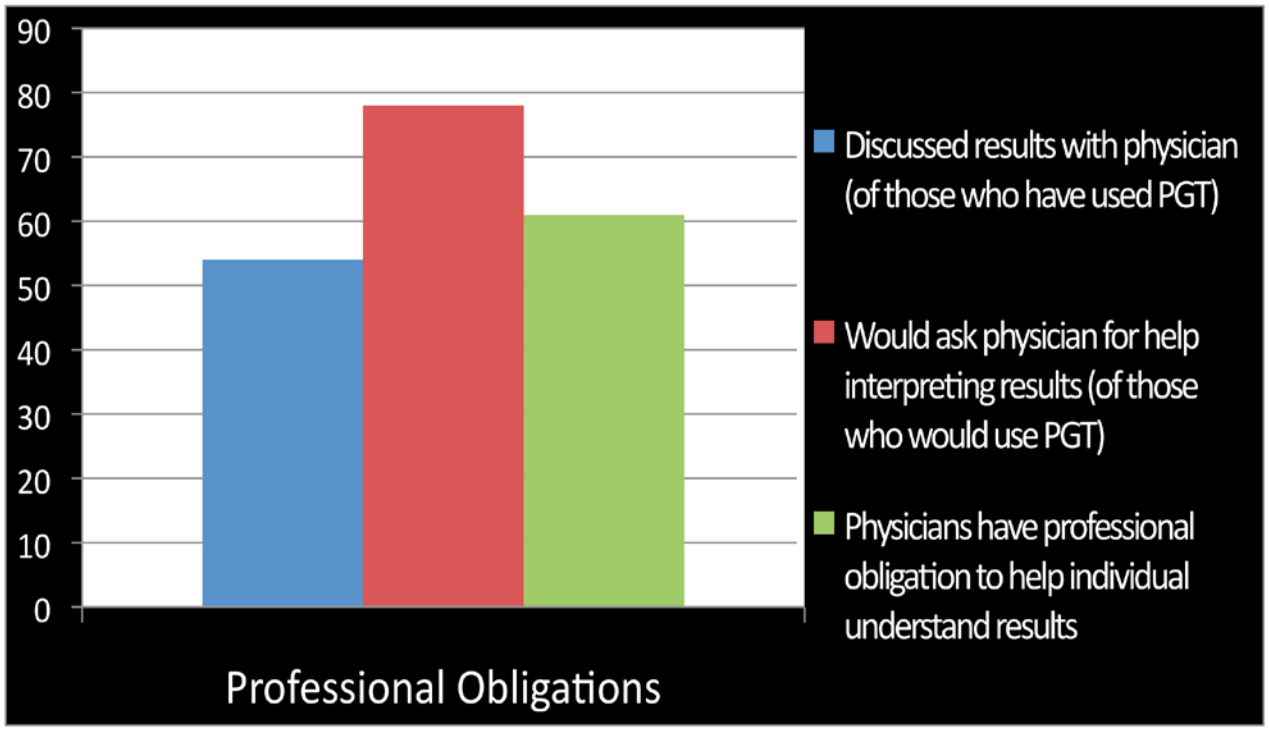
Online survey: Facebook.com **users** (2008)

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









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

sel patients accordingly. 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,[5] 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

Healthcare Ethics

SCIENCE AND REGULATION

Regulating Direct-to-Consumer Personal Genome Testing

International cooperation and postmarket regulation are needed for Internet-based direct-to-consumer genome tests.

Amy L. McGuire,[1]* Barbara J. Evans,[2] Timothy Caulfield,[3] Wylie Burke[4]

Direct-to-consumer (DTC) personal genome tests claim to provide consumers access to information about their genetic ancestry, susceptibility to traits such as excessive earwax, carrier status for diseases like cystic fibrosis, ability to metabolize drugs like statins, and likelihood of developing diseases such as cancer, Alzheimer's disease, and diabetes—all in one test, for a few hundred dollars, and without involvement of a health-care professional. Proponents of such tests tout the power of making such information easily available, while critics worry about consumer safety and harm that could result from unreliable tests, excessive claims about the meaning of tests or the benefits of being tested, and misinterpretation of test results (*1*, *2*). The U.S. Government Accountability Office (GAO) raised concerns (*3*, *4*), and the U.S. Federal Trade Commission (FTC) warned consumers to interpret at-home genetic tests with "a

U.S. Federal Regulation

Laboratories that provide clinical testing services in the United States—such as diagnostic or genetic testing—are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (*8*). The CLIA regulations address 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 (*9*). 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 itself 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 premarket 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

No one regulatory strategy will be

Law/Policy

Expansion


NIAAA
National Institute on Alcohol Abuse and Alcoholism
National Heart Lung and Blood Institute
NIBIB
NATIONAL CANCER INSTITUTE
NIMH
National Institute of Mental Health
NLM
ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS

Data Sharing

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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

- November 16, 2007 - See Notice (NOT-OD-08-013) Implementation Guidance and Instructions for Applicants.
- 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).
- May 15, 2006 (NOT-OD-06-071) - Notice to Applicants for NIH Genome-Wide Association Studies.

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National Institutes of Health (NIH) (http://www.nih.gov)

Sequencing

The Wellcome Trust Report:
Sharing Data From Large-Scale Biological Research Projects - 2003: A System of Tripartite Responsibility

GENETICS

No Longer De-Identified

Sequencing human DNA to discover genetic variation should be governed by existing regulations for human subjects.

Amy L. McGuire[1]* and Richard A. Gibbs[2]

As DNA sequencing becomes more affordable and less time-consuming, scientists are adding DNA banking and analysis to research protocols, resulting in new disease-specific DNA databases. A major ethical and policy question will be whether and how much information about a particular individual's DNA sequence ought to be publicly accessible.

Without privacy protection, public trust will be compromised, and the scientific and medical potential of the technology will not be realized. However, scientific utility grows with increased access to sequenced DNA. At present, ethical concerns about the privacy of subjects whose sequenced DNA is publicly released have largely been addressed by ensuring that the data are "de-identified" and that confidentiality is maintained (*1*–*2*). There is a large literature on the various data-management models and computer algorithms that can be used to provide access to genetic data while purportedly protecting privacy (*3*–*6*). We believe that minimizing risks to subjects through new developments in data and database structures is crucial and should continue to be explored, but that additional safeguards are required.

Scientists have been aware for years of the possibility that coded or "anonymized" sequenced DNA may be more readily linked to an individual as genetic databases proliferate (*1*, *3*, *7*, *8*). In 2004, Lin and colleagues demonstrated that an individual can be uniquely identified with access to just 75 single-nucleotide polymorphisms (SNPs) from that person (*9*). Genome-wide association studies routinely use more than 100,000 SNPs to genotype individuals. Although individual identification from the public release of these data would currently require a reference sample, the privacy risk associated with public data release is fueled by the extraordinary pace of technological developments and the rapid proliferation of electronic databases. If protective measures are not adopted now, public trust will be compromised, and genomic research will suffer.

Genetic sequencing typically involves three phases of investigation: (i) subject recruitment and sample collection (primary clinical investigation), (ii) DNA sequencing and data broadcast (genomic sequencing study), and (iii) data retrieval and analysis (secondary-use research) (see figure, above). Institutional Review Board (IRB) oversight and informed consent are unambiguously required for the first phase of sample collection, because it clearly involves human subjects research. There are also detailed consent requirements for some large-scale sequencing studies, such as the HapMap project, that cover the second and third phases. However, it is our experience that, in general, the consent process for most disease-specific genetic research is not protective for these phases and that the privacy risks associated with public data-sharing are not stated. Consent for these studies is highly variable, and in most cases, subjects are simply told that genetic analysis will be performed, without any explanation of what that means or with whom the resulting data will be shared. Further, participants are typically not offered the opportunity to participate in the research if they do not want their data publicly broadcast (*10*).

In the United States, there are now two federal regulations that could potentially apply to such studies—the Common Rule, which regulates all federally funded research and sets forth the federal policy for the protection of human research subjects (*11*) and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, which restricts certain unauthorized uses and disclosures of patients' identifiable protected health information by covered entities (*12*). Neither one specifically mandates IRB oversight or subject consent for the public release of sequenced data. The Common Rule would not apply if genomic sequencing studies were not considered to constitute human subjects research. Human subjects research is defined under the Common Rule as research involving "an individual about whom the investigator … obtains data through intervention or interaction with the individual, or identifiable private information" (*11*). According to a guidance document published in 2004 by the Office for Human Research Protections (OHRP), because the data are collected and coded by the primary clinical investigator, and the sequencing investigator is prohibited from deciphering the code, the data are not considered identifi-

From subject to data analysis. A typical medical genomic sequencing study.

CREDITS: GETTY IMAGES

[1]Center for Medical Ethics and Health Policy, Baylor College of Medicine, [2]Human Genome Sequencing Center, Baylor College of Medicine, One Baylor Plaza, Suite 310D, Houston, TX 77030, USA. *Author for correspondence. E-mail: amcguire@bcm.edu

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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."

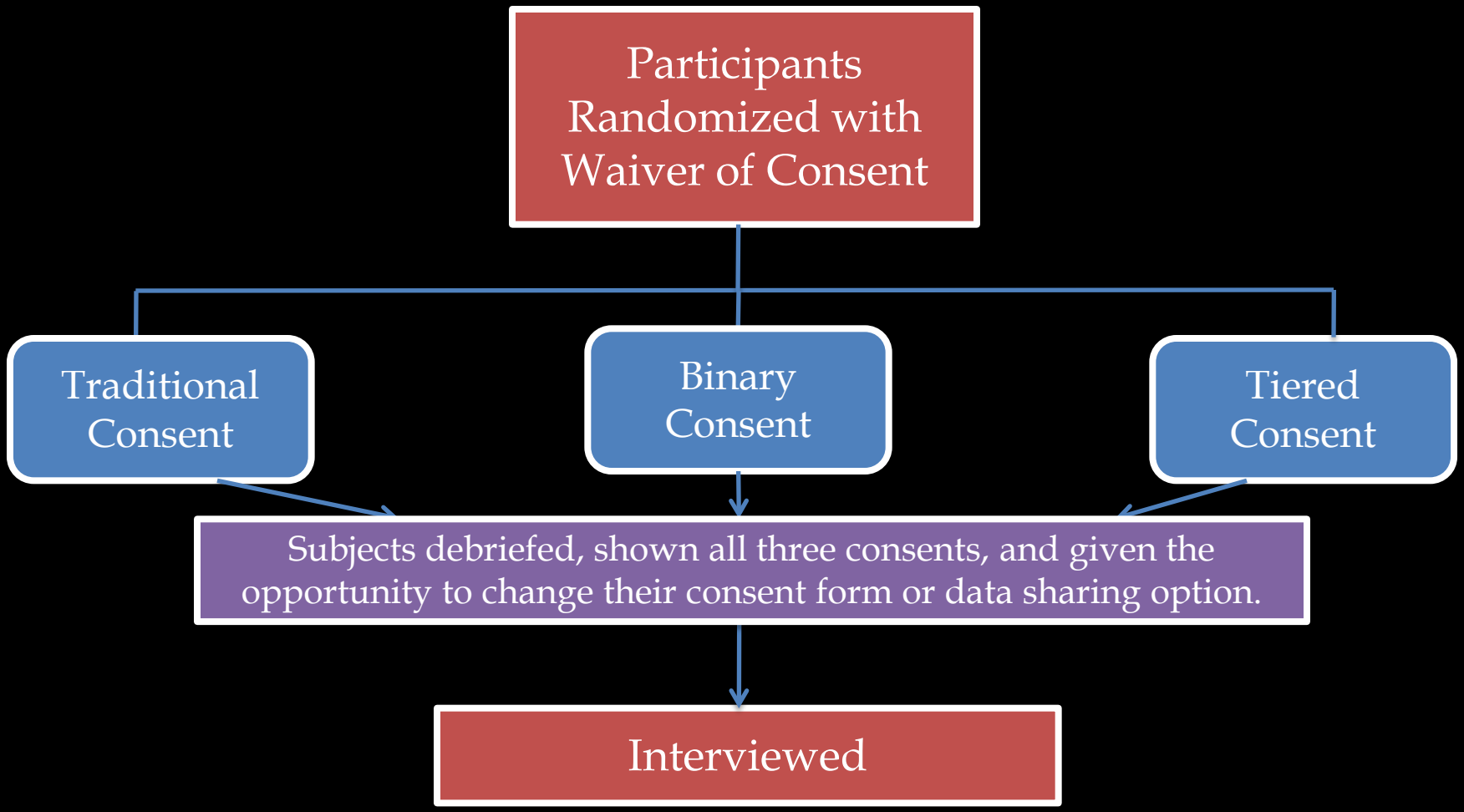
Policy Concerns

- 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

I.S. Kohane and R.B. Altman. Health Information Altruists – A Potentially Critical Resource. *NEJM* (2005).

Randomized Trial of Consent for Data Sharing

R01 HG004333 (2007-2011)



Planning for the Future of ELSI

Integration

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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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