Consent to What?!
Ethical and Policy Issues in Biobanking and Biospecimen Research

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What Is A Biobank?

- Any collection of biospecimens or genetic material
  - with or without associated data
- Retained for sharing and/or future uses
- May be with or without identifiers
- May be “de jure”
  - biorepository designed for storage and sharing
  - REB-approved scope, consent forms, oversight
- May be “de facto”
  - materials kept in lab freezer = accidental bank
  - casual sharing creates accidental bank
- You are a biobanker if you have:
  - kept any specimens beyond clinical need or after the end of the study
  - used any specimens for purposes not related to the purpose of initial collection
  - shared any specimens with anyone else

The Biobanking Boom

Big banks needed/wanted:

- **HapMap project**
- **gene-environment interactions**
- **Genome-Wide Association Studies**
- **Newborn blood spots**
- **All hospitalized persons**
- **Families with a disease or condition worldwide**
- **Statewide & national disease registries**
- **Adding biospecimen collection to large longitudinal studies**
- **Linking to medical records and other phenotypic data, continually updated**

Banking Specimens for Future Research

- **Why? Where? For how long? Who has access?**
- **With or without identifiers? Re-contact?**
- **Setting up a research biobank must have REB approval**
- **But what about using the biobank?**
  - **if user cannot access identifiers**
  - **perception: risks of harm to individual subjects are low**
- **Continued oversight needed**

"IOC to Store Athletes' Test Samples for Eight Years"

- --A. J. Perez, USA Today, 28 July 2008
- Previously, samples were stored for 30 or 90 days
- New rule makes Beijing Olympic athletes subject to results of new tests developed anytime during the 8-year period, which matches WADA's statute of limitations

New Technologies, New Capacities, New Questions

What do biospecimen providers need to know?

What should they be told?

What role should they play?

Critical Issues to Examine

- Confidentiality & Privacy
- Return of Results & Incidental Findings
- Interpretation & Dissemination of Results
- Group Interests
- Informed Consent
- Ownership & Control

Is Confidentiality Desirable?

- Legal protections from genetic discrimination are (no surprise) incomplete
- De-identification may sometimes make data less useful
- PGP: "We believe individuals from the general public have a vital role to play in making personal genomes useful. We are recruiting volunteers who are willing to share their genome sequence and many types of personal information with the research community and the general public, so that together we will be better able to advance our understanding of genetic and environmental contributions to human traits and to improve our ability to diagnose, treat, and prevent illness."
  - www.personalgenomes.org

Research with Genetic & Phenotypic Information

- **Confidentiality vs. "De-Identification"**
  - **Large data sets combine genetic data with phenotypic data, and continually link new data**
  - **Data-sharing plans spread information widely**
- **Risks of Harm to Individuals & Groups**
  - **Large data sets merge and research questions change over time**
  - **Who monitors whether changes in scope change risks or affect willingness to continue research contribution?**

GENETICS

No Longer De-Identified

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

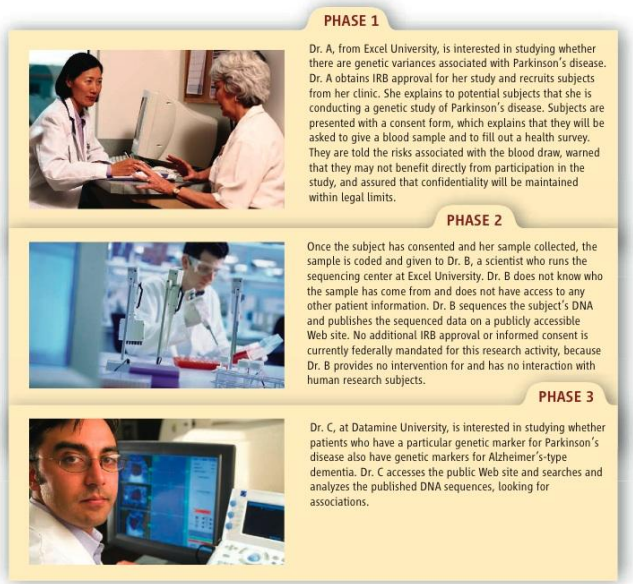
Amy L. McGuire[1]* and Richard A. Gibbs[2]

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)



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

(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-

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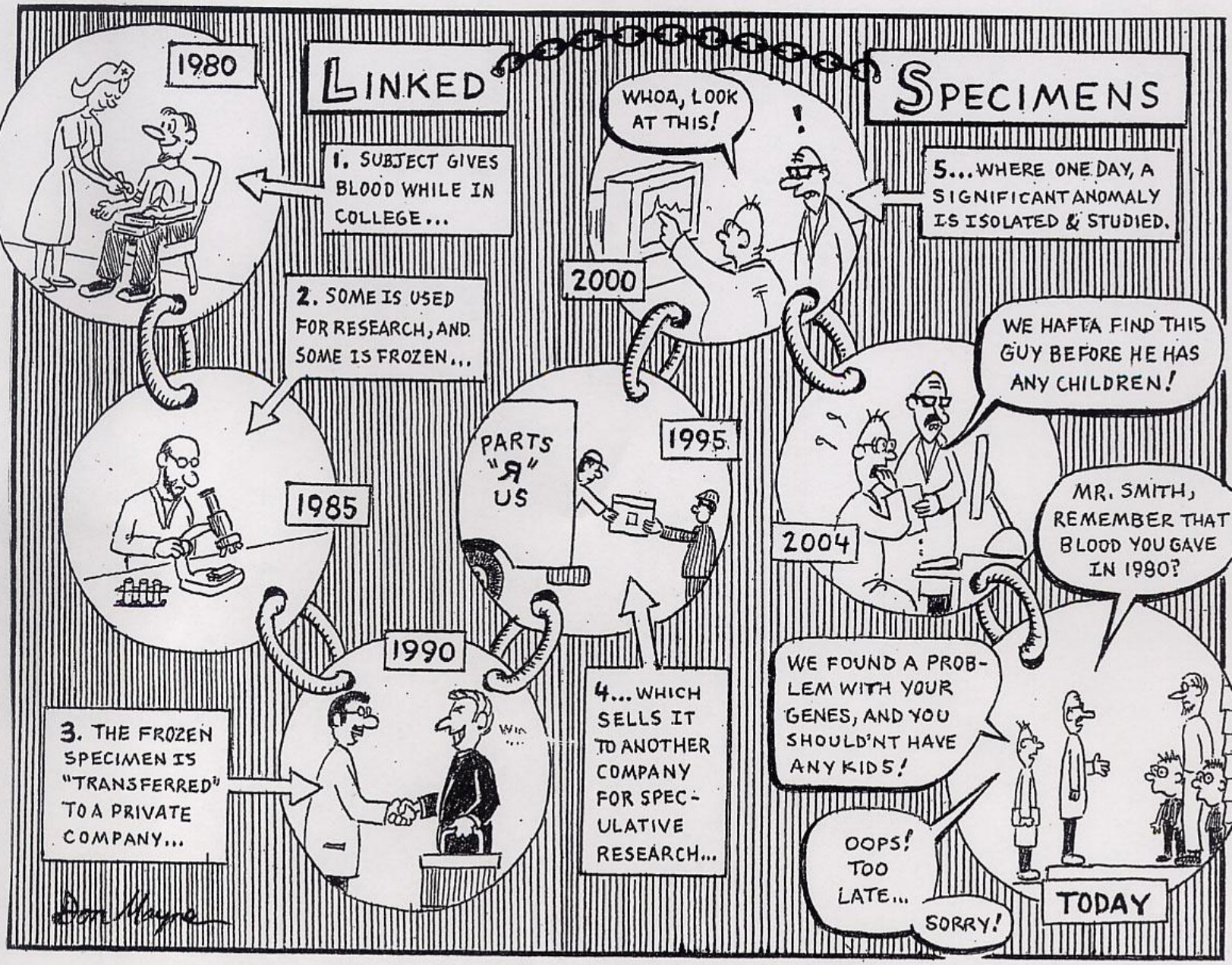
Is Confidentiality Possible?

- Can confidentiality be preserved when re-identification is increasingly possible?
- Ongoing data linkage:
  - how to safeguard sensitive information?
  - how to enable continuing data collection?
  - monitoring the balance
- Harms to individuals versus harms to groups
- Role of the REB:
  - require improved data security?
  - require improved risk disclosure?
  - both? neither? other?

Returning Results & Incidental Findings

- **Can confidentiality be preserved when re-identification is increasingly wanted?**
- **Recontact if medically significant information is found?**
  - **what is significant – and who decides?**
    - **nature, magnitude, likelihood, timeliness**
  - **privacy tradeoffs**
    - **how long is contact information kept?**
  - **whose duty is this?**
    - **who has the knowledge to determine medical significance?**
    - **contact information and knowledge may be widely separated**
  - **information and oversight infrastructure could be extensive (and expensive)**


LINKED
SPECIMENS
1980
1. SUBJECT GIVES BLOOD WHILE IN COLLEGE...
2. SOME IS USED FOR RESEARCH, AND SOME IS FROZEN...
1985
3. THE FROZEN SPECIMEN IS "TRANSFERRED" TO A PRIVATE COMPANY...
1990
4... WHICH SELLS IT TO ANOTHER COMPANY FOR SPECULATIVE RESEARCH...
PARTS "R" US
1995
2000
WHOA, LOOK AT THIS!
5... WHERE ONE DAY, A SIGNIFICANT ANOMALY IS ISOLATED & STUDIED.
2004
WE HAFTA FIND THIS GUY BEFORE HE HAS ANY CHILDREN!
MR. SMITH, REMEMBER THAT BLOOD YOU GAVE IN 1980?
WE FOUND A PROBLEM WITH YOUR GENES, AND YOU SHOULDN'T HAVE ANY KIDS!
OOPS! TOO LATE... SORRY!
TODAY
Don Mayer

Interpretation & Dissemination of Findings

- **Group interests and group harms**
  - **REBs often do not consider, but their significance is acknowledged (and growing)**
- **Dissemination of research results:**
  - **How should results be described?**
    - **race/ethnicity categories are inadequate or pernicious**
    - **“personalized genome” is a long way off**
  - **Duties of investigators, sponsors, institutions?**
    - **communicating with public about meaning (and limits) of genetic information**

Should Groups Have a Research Voice?

- Group rights & interests
- Individuals' choices about scope of research using information from them may (should?) reflect concerns about groups even when individuals are not identifiable:
  - individuals with family histories of stigmatized conditions
  - African-Americans, Native Americans, Ashkenazi Jews, other First Peoples & racial or ethnic groups
- Reporting and dissemination can stigmatize and foster discrimination

news feature

When two tribes go to war

Medical geneticists and isolated Native American communities afflicted by inherited diseases should have much to gain from working together. But the relationship can go sour, as Rex Dalton finds out.

C. KARNOW/CORBIS

South of the Grand Canyon in Arizona, in a valley that roads still don't reach, the Havasupai tribe has for centuries lived a cloistered existence in the high desert. Isolation in a geological wonderland has allowed the tribe's 600-plus current members to protect their ancient culture. But the flipside is a restricted gene pool that has given the Havasupai one of the highest incidences of type 2 diabetes anywhere in the world.

Such populations offer geneticists the chance to discover rare gene variants underlying disease that would be difficult to detect in more diverse groups. And in the early 1990s, with the tribe's blessing, a team from Arizona State University (ASU) in Tempe began searching for a genetic cause of the Havasupai's diabetes.

Instead of a genetic breakthrough, the research project has spawned lawsuits claiming $75 million in damages, filed by tribal members who claim that their rights were

240 kilometres northwest of Flagstaff, is closed to researchers.

"What concerns me deeply is that the allegations have resulted in a moratorium on biomedical research on the Havasupai reservation, excluding this and other communities from discoveries with the potential to address their health concerns," says Therese Markow, who led the Havasupai project during her years at ASU, and is now at the University of Arizona in Tucson.

Family roots

To investigate the genetics of disease in small, remote populations, it is important to determine just how genetically isolated a group really is. With modern molecular tools, researchers can

> "Native American tribes are so understudied. If this litigation continues, all research is going to cease."
> — Daniel Garrigan

revenue, and has made native tribes a political force. Given their remote location, the Havasupai do not run a casino, but they share in revenue from those Arizona tribes that do. And the state's tribes work together on various issues, hiring well-connected lobbyists and high-powered attorneys to protect their collective interests.

The growing influence of Native American tribes has already been used to block the publication of studies deemed culturally offensive — a development that has split researchers working with native communities (see 'The heart of the matter', overleaf). Some see it as unacceptable censorship; others argue that the tribes' cultural sensitivities must come first.

Information and Identity

- ***Havasupai Tribe v. Arizona State University***
  - "just stuff" (U.S. perspective)
  - "I saw my mother" (Maori health researcher studying anonymized medical records)
- **Genetic essentialism & group identification**
  - disease to personality trait to behavior
  - nature + nurture + culture
- **Who is responsible for responsible description & dissemination?** (abstract example)

Informed Consent: Scope?

- individuals deserve to know they may be contributing to research
- opt-out mechanisms?
  - initial choice vs. changed research scope
- public deserves to know value of research using biorepositories & combining genetic and phenotypic data
- how should groups be involved?
- Havasupai consent form example

Ownership & Control

- **Who owns your DNA? Is ownership the right term?**
  - The research subject who provides biospecimens to the biobank?
  - The investigator whose study collects them?
  - The bank that extracts, processes, catalogues, and stores them?
  - The investigator who withdraws them from the bank for further study?
  - The institution (e.g., university or industry) that houses and supports the biobank?
- **Can future uses be monitored & controlled?**
  - Recordkeeping burden, privacy risk
  - New IT + willingness + creativity = control?

A Citizenship Model for Biobanking & Research

- **protection model**
  - **analogy to patients**
  - **focus on rights & limiting power**
  - **limited consent**
- **utility model**
  - **analogy to consumers**
  - **focus on data security & public health**
  - **blanket consent**
- **citizenship model**
  - **agency, awareness, democratic engagement**
  - **focus on increasing science literacy, database transparency**
  - **broad consent with opt-out mechanism**
    - ***--Vilhjalmur Arnason, University of Iceland***

Approaches to Informed Consent for Research on Stored Biospecimens

- **Specific consent:**
  - Research participants are recontacted and asked to consent for each new use of their specimen or information that is outside the scope of the original consent.
- **Tiered consent:**
  - At the time samples are collected, research participants are presented with a menu of options from which to choose, e.g., general permission for future use, consent only for future uses related to the original study topic, consent for future uses unrelated to the original study topic, and requiring investigators to obtain specific consent for any future use that differs from the original study.
- **General permission:**
  - At the time samples are collected, research participants are asked to permit all future uses that a qualified ethical review board determines to be scientifically meritorious and ethically defensible.
- **Presumed consent:**
  - At the time samples are collected, research participants are informed that their specimens will be used in future research unless they expressly deny permission.

--Mello MM & Wolf LE: The Havasupai Indian Tribe Case -- Lessons for Research Involving Stored Biologic Samples. NEJM 2010;363:204-207

Conclusions & Recommendations

- Utility of research using biospecimens and genetic/phenotypic data is not sufficient justification for minimal oversight of downstream data sharing and new uses
- Informing & involving public can increase science literacy without constraining researchers
- Awareness of data sensitivity, for both individuals & groups, can increase both researcher understanding & public trust
- Bioinformatics has capacity to tag & tailor research uses to benefit both public health & public interest