Ethics of Genetic Research
Stored Samples

Henry Silverman, MD, MA
Professor of Medicine
University of Maryland, USA
Objectives

• Research Definitions
• Research on Stored Samples
• Stem Cell Research
• Genetic Testing
• MERETI Program
Genetic Disease in Arab world

• High prevalence of genetic disease in Arabs

• Consanguineous marriages
  – 30% -60% of all marriages
  – Increases incidences of recessive disorders

• Consanguinity Continues
  – Couples refuse advice of premarital screening
  – Pre-implantation genetic diagnosis not available
What Is So Special About Genetic Information?

– Genetic information
  • Is about individual identity (genes are determinative of human health and behavior)
  • Is about families
  • Highly predictive of future health.

– Interventions to enhance genetic traits
  • allow control of which kinds of children will be born, raising eugenic concerns.
Benefits of Genetic Research

• Identify gene variations associated with diseases
  – Clarify disease risks
  – Develop new diagnostic tests
  – Develop targeted treatments for specific diseases

• Personalized Medicine
  – Determine why drugs are effective on certain individuals but not on others.
Review Research Definitions
Is it “Research”?
... a **systematic** investigation, including research development, testing and evaluation, **designed** to develop or contribute to “**generalizable**” knowledge.

Widespread information...
Are there “Human Subjects”?
A research involving living individuals about whom the researcher obtains:

- Data through intervention or interaction
- Identifiable private information

OR

Prospective Data

Existing Data
What are the Ethical Concerns?

- Informed consent
- IRB Review
- Confidentiality Risks
  - Individuals
What are the Ethical Concerns?

• Informed consent
  – Existing Samples
  – Future use of samples

• Confidentiality risks to individuals
  – Family members
  – Community Harms

• IRB Review

• Disclosure of research results to participants
• Ownership of samples
Research on Stored Tissue Samples: What are the Ethical Issues?
Existing samples: Informed Consent??

• Previous informed consent to a specific project has NOT been obtained
  – previously collected for clinical purposes
  – previously collected for another research study
Case #1

• An investigator wants to do an epidemiologic study of the prevalence of breast cancer in a country. She wants to obtain the biopsy samples that were obtained from patients during the last five years in all of the hospitals.

• Should the investigator re-contact the previous patients for their informed consent?
Existing samples: Informed Consent

Previous informed consent to a specific project has NOT been obtained

- Re-contact all donors

- Make samples de-identified
  - Non-Human Subjects Research (limits value)

- Waive Informed Consent
  - Confidentiality procedures are such that research can be considered minimal risk
Choices

• Re-Contact Participants
  – Autonomy interests of the research participants requires express permission or some other precautions for additional procedures.

• Non-Human Subjects Research
  – De-identified

• Waive Informed Consent
  – Public good of unrestricted biorepository research outweighs the rights of individual participants to choose
  – research is minimal risk and it is impracticable to re-contact.
Criteria for Waiver of Consent

Existing Data

• The research presents no greater than minimal risks.

• Obtaining informed consent is not practicable.
• Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
Havasupai tribe vs. Arizona State University

• The Havasupai are Native Americans who live at the base of the Grand Canyon off of the Colorado River.
• Their creation story is that the Grand Canyon was created as waters receded from a global flood and became the birthplace of all humans.
Original Diabetes Study

- Rate of diabetes is 55% among women and 38% among men.
- In 1989, members of Havasupai tribe approached Arizona State University (ASU) to determine if a genetic link is present.
- Approximately 100 tribal members signed a broad consent to “study the causes of behavioral/medical disorders”.
- For most tribe members, English was a second language.
- All believed they donating blood solely for the purpose of looking for a link to diabetes.
- ASU researchers determined that a genetic link to diabetes did not exist.
Continued Research on Existing Samples

- ASU researchers conducted other research on the samples provided by the tribe without obtaining additional consent.
- Alcoholism and the origin and migration of the tribe from Asia.
- Carletta Tilousi, a member of the Havasupai Tribe was a graduate student at ASU
- She attended a presentation on research done on the blood samples.
- She became upset when she heard her tribe described as an isolated group whose ancestors had migrated to Arizona from Asia.
- Tilousi felt the blood of her people had been “used” to challenge their identity.
Havasupai vs. Arizona State University

• In 2004 the Havasupai Tribal Council filed a law suit against ASU.
• After seven years of litigation, the Havasupai Tribe settled in April 2010.
• Terms of settlement
  – Payment of $700,000
  – Return of the blood samples
  – Additional assistance including scholarships and help in obtaining federal funding for a health clinic
Risks of Genetic Research

• Individual harms
• Group Harms
Research Involving Prospective Collection of Tissue Samples for Future Unspecified Research
What are the Ethical Issues?

• How should Informed Consent be obtained?
• What are the risks to individuals?
• What are the risks to ethnic groups from genetic research?
• Do participants have a right to withdraw their samples?
• Who owns the samples?
• Who shares in commercial profits?
Welcome to UK Biobank

Have you received your letter inviting you to participate in UK Biobank? Taking part in UK Biobank's unique research project is easy to do. You can confirm your appointment time (or cancel it) online now. Just click the 'confirm' button below or above. A map and more information about your visit to an assessment centre are also a click away. If you want more information or to change your appointment time, that's simple too - just call our Participant Resource Centre on the number above (Monday to Saturday 8am-7pm, calls are recorded). UK Biobank has Quality Management System Standard ISO 9001:2008 accreditation.

If you are looking for more information about the project, just follow the links on the left.

Winter weather - thank you to all those participants who have struggled through the bad weather to make their appointment. If you are unable to attend, please remember to rearrange your appointment by calling our free phone help line on 0800 0 276 276.

433,852 people are already helping.
11pm Wednesday 3 March 2010
Informed Consent Issues

• Specific Consent
  – Only on the disease that is focus of the study

• Broad Consent:
  – All future diseases

• Tiered Consent: Choices
  – Range of diseases
  – Samples de-identified or coded
  – Re-contact for future research
What are Participants Actual Choices?

<table>
<thead>
<tr>
<th>Condition</th>
<th>N=1298</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline all Future Research</td>
<td>7%</td>
</tr>
<tr>
<td>Consent to Future Research on Same Condition</td>
<td>91%</td>
</tr>
<tr>
<td>Consent to Future Research on ANY Condition</td>
<td>87%</td>
</tr>
</tbody>
</table>

Most research participants authorize the unlimited future research use of their biological samples

Chen et.al., 2005; Arch Intern Med.
Proposed Model

• Binary choice of
  – refusal or
  – broad and future consent (unspecific conditions).

• Confidentiality Safeguards
  – De-identify samples
  – Establish rules for relinking de-identified samples
  – Establishing security measures to minimize unauthorized access to samples and associated data

• RECs approve new studies.

• Can withdraw consent at anytime
May the University of Maryland collect and store your tissue samples after the end of this research for use in future research?

- YES, my sample may be saved for future <specify a specific condition/disease> research
- NO, my sample must be destroyed at the end of this research project
Binary Model

• If yes, may the University of Maryland keep your name and other identifying information with your samples?

☐ YES, my personal identifiers and medical information can be kept with my samples. All information will be kept secure and confidential

☐ NO, my name and identifiers must be removed from my samples. My samples cannot be linked back to me
Disclosure of Genetic Results

• Should research participants be told the results of the genetic analysis on their bio samples?
Disclosure of Genetic Results

Reasons Given in ICFs for Non-Disclosure

• Meaning of results would be unclear
• Results would not confer a benefit
• Tests are experimental
• Non-disclosure provides protection against discrimination
• Impossible, as data would be de-identified
• Privacy implications for family members who did not provide samples.
Disclosure of Genetic Results

• Practice of not giving individuals the results of genetic research is changing.

• Many commentators now argue that there are legal/ethical obligations to give results under certain circumstances/conditions:
  – When proven therapeutic or preventive interventions are available
  – Associated risk for the disease is significant
  – When the disease has significant reproductive implications
Ownership of Tissue Samples

• Who should own the tissue samples?
  – Investigators?
  – Institution?
  – Research Participants
Collection, storage and use of blood samples for future research: views of Egyptian patients expressed in a cross-sectional survey

Alaa Abou-Zeid,1 Henry Silverman,2 Magdi Shehata,3 Mohamed Shams,4 Mervat Elshabrawy,5 Tamer Hifnawy,6 Safa Abdel Rahman,7 Bahiga Galal,8 Hany Sleem,9 Nabil Mikhail,10 Nadia Moharram11

• Methods:
  – Survey distributed to patients in rural, urban, public, and private hospitals
  – Public and private clinics
  – N = 600
<table>
<thead>
<tr>
<th>Statement</th>
<th>% Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent forms should provide an option for collection of blood samples for future research</td>
<td>44.3</td>
</tr>
<tr>
<td>Future research should be restricted to the illness being studied</td>
<td>39.9</td>
</tr>
<tr>
<td>future research does not have to be restricted to the illness being studied</td>
<td>54.0</td>
</tr>
<tr>
<td>Statement</td>
<td>% Agree</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Give to other researchers without re-contact</td>
<td>53.3</td>
</tr>
<tr>
<td>Time limit for storage of samples</td>
<td>21.7</td>
</tr>
<tr>
<td>Right to withdraw blood samples</td>
<td>28.8</td>
</tr>
<tr>
<td>Right to share in profits</td>
<td>32.8</td>
</tr>
<tr>
<td>Results should be given back to participants</td>
<td>88.8</td>
</tr>
<tr>
<td>Samples may be used for future genetic research</td>
<td>66.2</td>
</tr>
<tr>
<td>Statement</td>
<td>% Agree</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Samples may be sent to another Arab country</td>
<td>62.0</td>
</tr>
<tr>
<td>Samples may be sent to a European country</td>
<td>41.8</td>
</tr>
<tr>
<td>Samples may be sent to the USA</td>
<td>37.0</td>
</tr>
<tr>
<td>Gov’t approval for sample exportation</td>
<td>88.2</td>
</tr>
</tbody>
</table>
Role of IRBs
Prospective Collection of Samples
Elements of Informed Consent

1. Whether or not subjects will be re-contacted
   • to provide informed consent for each new study that will be performed on the blood samples.

2. Adverse consequences of a breach of confidentiality
   • loss of insurance or employment

3. How long the blood samples will be stored.

4. Whether or not subjects will be re-contacted
   • regarding future research findings relevant to their health.

5. Whether subjects may withdraw their samples from future research.

6. Whether subjects will share in any profits
   • that might result from any commercial product derived from the samples.

7. Limits on future use of the samples to a particular institution, researcher, area of study, or country
### Table 3: Text of provisions and mean percentages for which each provision was reported as included in consent forms

<table>
<thead>
<tr>
<th>Provision</th>
<th>N</th>
<th>Mean %</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>The extent to which confidentiality can or will be maintained in future research performed using the samples</td>
<td>285</td>
<td>95</td>
<td>20</td>
</tr>
<tr>
<td>How subjects may withdraw their samples from future research</td>
<td>251</td>
<td>72</td>
<td>43</td>
</tr>
<tr>
<td>Separate consent for the collection, storage, and future use of blood or tissue samples</td>
<td>281</td>
<td>70</td>
<td>43</td>
</tr>
<tr>
<td>Whether subjects will be recontacted regarding future research findings relevant to their health</td>
<td>240</td>
<td>69</td>
<td>43</td>
</tr>
<tr>
<td>Limits on future use of the samples to a particular institution, researchers, or area of study</td>
<td>249</td>
<td>68</td>
<td>44</td>
</tr>
<tr>
<td>Whether subjects may have property interests in gene products derived from their blood or tissue samples</td>
<td>226</td>
<td>48</td>
<td>48</td>
</tr>
</tbody>
</table>
Actual Consent Form Options

- Clinical Research Centers (n = 139 studies)
- 95% stated that bio samples would be stored for future genetic research

Wolf LE, et.al. IRB. 2010; 32:7-18

<table>
<thead>
<tr>
<th>Consent Options of How Biosamples Could Be Used</th>
<th>% of ICFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Option that materials can be stored?</td>
<td>52.5</td>
</tr>
<tr>
<td>Whether participants will be contacted again in the future</td>
<td>31.7</td>
</tr>
<tr>
<td>Whether materials can be used for genetic testing</td>
<td>25.2</td>
</tr>
<tr>
<td>Discussed limiting future research to specific conditions</td>
<td>69.1</td>
</tr>
<tr>
<td>Discussed confidentiality protections</td>
<td>95.7</td>
</tr>
<tr>
<td>Mentioned social and psychological risks</td>
<td>47.0</td>
</tr>
<tr>
<td>Mentioned that withdrawal of stored samples would be allowed</td>
<td>70.5</td>
</tr>
<tr>
<td>Mentioned whether participants would receive research results</td>
<td>64.0</td>
</tr>
<tr>
<td>Mentioned the commercial use of samples</td>
<td>53.0</td>
</tr>
</tbody>
</table>
شكرًا