RESPONSIBLE CONDUCT OF GENETIC RESEARCH

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Former Executive Chair, Institutional Review Boards
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Does it need to be an explosive issue?
Genetics Research -
What’s All the Fuss About?

Reasons why genetic research is treated specially:

1. Concern for Discrimination/Stigmatization
   • Potential to identify individuals at risk before disease develops
     – Potential for insurance and/or employment discrimination

2. Risk of suicide/depression
   • Can affect both those who are found to carry a mutation and those who do not
Genetics Research -
What’s All the Fuss About?

Reasons why genetic research is treated specially:

3. Information obtained from one individual may have predictive value for other family members
   • May adversely impact family relations
LDL receptor mutation present
Genetics Research -
What’s All the Fuss About?

Reasons why genetic research is treated specially:

4. Genetics is relatively new and many people do not understand it
   • Fear makes for good news stories
   • We shun what we fear
Are Genetically Engineered Foods Safe? GMOs have not been proven safe, and long-term health studies have not been conducted. A growing body of peer-reviewed studies has linked these foods to allergies, organ toxicity, and other health problems.
Categories of Genetics Research Activities

1. Collection of pedigrees (family trees)
2. Recruitment of family members
3. Research involving specific racial/ethnic groups or other defined populations
4. Collection of specimens for DNA isolation and storage
5. Drawing the line between research and clinical care
6. Gene therapy
Pedigree collection:
Vital for the research, but does collection of information about family members who have not consented to participate constitute invasion of privacy?

In the clinical setting, we are asked questions about our family history all the time.

*What makes research different?*
*Who ‘owns’ your family history?*
The use of private information for the well-being of a patient is considered justified but in research, we are held to a higher standard.

The risk of a breach of confidentiality strictly for the benefit of research may not be justified.

Apply the standard of the 'minimally necessary' information for research.
Sarah Jones, 58 yr. local
Tel 555-1134

Tom Jones, BD 11/2/44
d. 43 yrs. MI St. Louis

Mary Smith, 29 yr.
Detroit

Susan Jones, 27 yr.
St. Louis

Mark Jones, 62 yr.
St. Louis

Emily Gray, 61 yr.
‘High cholesterol’
lives in Smithville, OH

Bill Jones 34 yr.
‘High cholesterol’
coming to visit from Montreal next April

Mary Smith, Susan Jones,
29 yr. 27 yr.
Detroit St. Louis

Timothy Jones
Angioplasty at 36 yr.
lives with mother

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Angioplasty

‘High cholesterol’
Maintenance of confidentiality of family history information is paramount

- Investigators must provide the IRB with detailed descriptions of how the privacy of these records will be protected
- Some types of information may be of such a sensitive nature as to be inappropriate to collect even in an indirect fashion without the consent of all subjects
- Consideration should be given to obtaining a Certificate of Confidentiality
Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
2. Research involving recruitment of family members

- Can investigators collect contact information for family members without their consent?
- Typical IRB recommendation – provide written information containing phone numbers for the investigators to be distributed to family members, and the family member can contact the research team
  
  - What is the chance that anyone will call, even if they are interested in the research?
• Can the index case (proband) contact family members and obtain verbal consent to release contact information to investigators?

*What is the potential for coercion?*
3. Research involving specific racial/ethnic groups or other defined populations
   - Population stigmatization
   - Cultural differences in consent
   - Dealing with different perceptions in non-Westernized cultures
Jewish leaders seek genetic guidelines...

“...a growing list of mutations in the Ashkenazi population linked to disease, including Tay Sachs, Gaucher's and the 185delAG mutation associated with breast and ovarian cancer.

Such findings, which have already led to Jewish groups being targeted as a potential market for commercial genetic tests, could create the perception that Jewish people are unusually susceptible to disease, says Rutkin.

As a result, she warns, anyone with a Jewish-sounding last name could face discrimination in insurance and employment as companies struggle to keep down health-care costs.”
Community Dimensions of Consent

“…in many developing country settings, consent may be invalid if it does not have a familial or communal dimension...However, tension may arise between individual and community consent; for example, if community elders decide that research should be participated in but individuals are unwilling, or if community leaders withhold consent but individuals want to participate.”

Consent in non-Westernized Cultures

- Is it appropriate to apply the same standards for informed consent in all cultures?

- How do you explain concepts such as genetic testing to someone from a primitive society?

- Who gives consent in a culture in which a woman’s father or spouse is viewed as having the authority to determine what she can or cannot do?
  - Even if you attempt to obtain consent directly from such a woman, how can you know if the consent is coerced?
As the Karitiana Indians remember it, the first researchers to draw their blood came here in the late 1970s, shortly after the Amazon tribe began sustained contact with the outside world. In 1996, another team visited, promising medicine if the Karitiana would just give more blood, so they dutifully lined up again.
But that promise was never fulfilled, and since then the world has expanded again for the Karitiana through the arrival of the Internet. Now they have been enraged by a simple discovery: their blood and DNA collected during that first visit are being sold by an American concern to scientists around the world for $85 a sample.
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**Line JK1388; Karitiana tribe; Tupi speaking from the Rondonia Province of Brazil; Yale-Stanford Collection**

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| **Pricing**| Commercial Pricing: $85.00  
Academic and not-for-profit pricing: $85.00 |

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| **Pricing**| Commercial Pricing: $55.00  
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**Forms Required for Ordering**
- Assurance Form (Must have current form on file)
- Order Form (Download if ordering by FAX)
- Statement of Research Intent Form (Download if ordering by FAX)
SUPAI, Ariz. — Seven years ago, the Havasupai Indians, who live amid the turquoise waterfalls and red cliffs miles deep in the Grand Canyon, issued a “banishment order” to keep Arizona State University employees from setting foot on their reservation — an ancient punishment for what they regarded as a genetic-era betrayal.
Ethics: DNA Returned to Tribe, Raising Questions About Consent

Jennifer Couzin-Frankel

Tribe members charged that their DNA had been collected by university researchers without proper consent; after a 6-year legal battle, the university has now agreed—among other concessions—to return more than 100 DNA samples to the Havasupai and pay $700,000.

Although some tribe members had signed consent forms allowing blood samples collected 20 years ago to be studied broadly, they claimed in court that they had been told that the DNA would be used only for diabetes research.

In fact, the data were used for a variety of studies.
4. Research involving collection of specimens for DNA isolation and storage
   - Sharing of specimens with other investigators
   - Long term storage of specimens
   - Dealing with potentially clinically relevant results
• Many research studies involve long term storage of DNA samples or cell lines
• This may be beneficial for subjects (multiple studies may be performed without the need to request additional samples) and investigators (ability to perform ‘freezer studies’ to test new candidate genes, etc.)
  • **Who decides for what studies a given specimen can be used?**
  • **What types of safeguards are needed to protect subject privacy?**
Permission to share my sample(s) with other researchers?

I give permission for the research team to share my sample with the individuals noted below:

YES ☐ NO ☐ Researchers at CSMC studying (state disease)

YES ☐ NO ☐ Researchers at other institutions studying (state disease)

YES ☐ NO ☐ Researchers at CSMC studying any disease

YES ☐ NO ☐ Researchers at other institutions studying any disease

YES ☐ NO ☐ In addition, I agree to be contacted in the future to receive information on other research studies investigating (state disease)
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YES [ ] NO [ ] [ X ] In addition, I agree to be contacted in the future to receive information on other research studies investigating (state disease)
• Do research subjects really understand the options?  
   Probably not

• Who do they want to make decisions about the future use of their samples?  
   The investigator who recruited them

• Will the decisions they make be respected?  
   This is tough to accomplish...
As part of this research, we will make your sample available to researchers at non-CSMC institutions who are studying the same disease as described in this consent form. Your sample will be shared with …..

The sample will be labeled with a unique study number that will link your identity so that only the research team can recognize you.

OR

The sample will not contain any information that could be used to identify you.
Privacy in Genetics Research
Genotyping in Genetics Research

- Genetic research has moved away from testing a handful of candidate genes based on an understanding of disease pathophysiology.
- Instead, large scale genotyping (genome wide association, GWAS) is frequently performed.
  - Typically entails genotyping ~700,000 to >1 million snp’s.
- Exome sequencing is now used extensively.
- Whole genome sequencing is coming soon.
• Genome Wide Association and sequencing generates huge amounts of data on each subject

• To maximize the knowledge resulting from such studies, NIH strongly encourages sharing of data
The NIH Policy on Genome Wide Association Data

If genome wide association is performed with NIH funding, the investigators are obligated to deposit the data in the dbGaP repository, where it can be made accessible to other investigators.

In order to minimize the risks to study participants, data will be submitted to the GWAS data repository without identifiable information and using a random, unique code.
The Fallacy: Is DNA de-identifiable?
“…an individual can be uniquely identified with access to just 75 single-nucleotide polymorphisms (SNPs) from that person.”

Amy L. McGuire and Richard A. Gibbs

SCIENCE 312:370-371
APRIL 21, 2006
With modern DNA technology, how can the anonymity of a research subject be protected?
A woman became pregnant using a sperm donor program
She knew donor’s birth date, birth place, and college degree
At 15, her son decided to try to learn about his background
For $296, the boy sent a cheek swab to FamilyTreeDNA.com, an online genealogy DNA-testing service
Contacted by 2 men with closely matched Y chromosomes
~ 50% chance that all 3 had the same father, grandfather, or great-grandfather
Both men had the same surname, but with different spellings
He purchased the names of everyone born in the same place on the same day from Omnitrace.com
One man had the surname he was looking for, and within 10 days he had made contact
Most individuals who contribute their DNA, some studies have found, want science to benefit broadly and are not interested in being contacted for additional consent. But others may feel differently.

In a study of Alzheimer's disease, participants were asked to give permission for their data to be put into dbGaP.

Of the 1340 surveyed, 88% consented, while 9.5% refused.

The researchers were struck that even those who agreed were grateful to have been asked.
Dealing with potentially clinically relevant results:

- At the time that many studies are initiated, the likelihood of finding clinically relevant results in the near future is small.

- If such results are generated, what is the investigator’s:
  - Obligation to recontact study subjects?
  - Ethical right to recontact study subjects?

- What should the investigator do if the research turns up something that is clinically relevant, *but far different from what was expected*?
Willingness to receive results of testing performed as part of research

YES ☐ ☐ NO ☐ ☐ I wish to receive information about the testing conducted on my sample

YES ☐ ☐ NO ☐ ☐ I wish to receive general information about the study results. I understand that this will not include specific information on the testing completed on my sample.

YES ☐ ☐ NO ☐ ☐ Should information that may be important to my health become available in the future, I would like to be contacted and given an opportunity to learn of this information. I understand that it is my responsibility to update any changes to my address information.
Can research participants really make an informed decision about their wish to receive results when those results may come many years later and when the nature of the results may not be predictable?
Can researchers give results generated in a research laboratory to research subjects?

Research labs typically do not have CLIA approval, meaning the test results do not meet federal standards for clinical laboratories.
Exome Sequencing is happening

Whole Genome Sequencing is on its way.......
Exome Capture
Minor allele frequency and coding indel length distributions.

Exome Sequencing Identifies the Cause of a Mendelian Disorder

**Miller Syndrome**

severe micrognathia, cleft lip and/or palate, hypoplasia or aplasia of the posterior elements of the limbs, coloboma of the eyelids and supernumerary nipples

*Ng et al, Nature Genetics 42:30–35 (2010)*
4 subjects with Miller syndrome were studied:

2 siblings

2 additional unrelated individuals
• Using exome sequencing data from these 4 individuals, a gene called DHODH was identified to cause Miller syndrome

• Unlike other reported cases of Miller syndrome, the siblings both had lung problems
• The second candidate gene, DNAH5, encodes a protein found in cilia, and mutations in DNAH5 are known to cause primary ciliary dyskinesia

• Thus, exome analysis revealed that both siblings actually have 2 genetic disorders, Miller syndrome and primary ciliary dyskinesia

Return of Results from Exome Sequencing

- How do you decide what is a disease causing mutation?
- How do you decide what results should be given to the study participant?
  - Actionable – i.e. something that would alter medical care
  - Something that might impact reproductive issues
  - Does the individual have a right to know under any circumstances?
6. Research involving gene therapy
Gene Therapy holds the potential both for curing and preventing diseases that we will otherwise never be able to treat effectively.

Gene therapy is risky - the technology is new and there is much we still do not understand:

- gene regulation
- the impact of random vector insertion into the genome
- the impact of germ line insertions of recombinant DNA

- Healthy volunteer – subject #18 (of 19)
- Dose finding gene therapy trial for ornithine transcarbamylase deficiency
- Attenuated adenovirus vector
- Fever shortly after gene infusion
- Liver failure after 1 day
- Died of multisystem organ failure after 4 days

Jesse Gelsinger, age 18, Tucson, AZ
Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients

Steven J. Howe,1 Marc R. Mansour,2 Kerstin Schwarzwälder,3 Cynthia Bartholomae,3 Michael Hubank,4 Helena Kempski,4,5 Martijn H. Brugman,6 Karin Pike-Overzet,7 Stephen J. Chatters,5 Dick de Ridder,7,8 Kimberly C. Gilmour,9 Stuart Adams,9 Susannah I. Thornhill,1 Kathryn L. Parsley,1,9 Frank J.T. Staal,7 Rosemary E. Gale,2 David C. Linch,2 Jinhua Bayford,9 Lucie Brown,9 Michelle Quaye,1 Christine Kinnon,1 Philip Andliff,9 David K. Webb,9 Manfred Schmidt,3 Christof von Kalle,3,10 H. Bobby Gaspar,1,9 and Adrian J. Thrasher1,9
Leber's congenital amaurosis (LCA), is a rare form of inherited blindness.

Researchers injected one eye of LCA patients with a virus carrying a gene coding for an enzyme needed to make a light-sensing pigment.

In the first completed trial, the light sensitivity of all 12 partially blind patients improved.

Four children gained enough vision to play sports and stop using learning aids at school.

Science 18 December 2009: Vol. 326. no. 5960, pp. 1600 - 1607
DOI: 10.1126/science.326.5960.1600
The challenge –

Deciding when experimental gene therapy is safe enough to be tested in humans
Now, it is your turn to talk........

Case Scenarios
1. Susan Jones, a 25 year old woman, was still living at home with her parents, as was her twin brother. Susan learned about a research study that was being conducted at a local university, which involved completing a questionnaire asking details of her medical history, along with information about her relatives. She thought this might be interesting, contacted the research team and, after hearing details about the study, agreed to participate. The investigator mailed a copy of the questionnaire to Susan to fill out. However, before Susan got home from work, her father, Tom Jones, opened the envelope, even though it was addressed to her. He became upset when he saw the type of questions that were being asked. In particular, he was upset when he saw questions asking whether her parents had ever suffered from depression or if they had abnormal genitalia.
The father contacted university officials, who assured him that the study had been reviewed by the IRB and that his daughter had provided informed consent when she enrolled in the study. However, the father was not satisfied and contacted the Office for Protection from Research Risks (OPRR; now the Office for Human Research Protections), which investigated his complaint. OPRR ruled that the IRB should have considered whether family members were human subjects of this research based on their relationships to the enrolled subjects, as well as the nature of the family information being collected. After review of the IRB procedures, the OPRR and the Food and Drug Administration suspended human subject research at the university, stating that the IRB had inadequately documented its monitoring of research protocols.
– Did the researchers have the right to include questions of this nature in the questionnaire?

– What if, instead of asking about psychiatric history and genitalia, the questions asked for parental history of hypertension and what their occupations were?

– In a medical setting, it is standard to ask information about family history of disease. Why might it be legitimate for her doctor to ask Susan these questions, but inappropriate for a researcher to ask them?
– What constitutes private information?

– What defines ‘identifiable information’? If Susan did not live at home with her parents, was married and used Smith as her last name, not Jones, would the information collected on her parents still be identifiable?

– Suppose the investigators had wanted to contact Susan’s parents and siblings to invite them to participate in the research. How should they have done so?
2. A large, multicenter clinical trial comparing a variety of treatments in patients with congestive heart failure was performed. The treatment tested in one arm of the study involved a combination of two cardiovascular medications, isosorbide dinitrate and hydralazine. Both of these medications have been FDA approved and used in treating heart failure for many years. Subjects in the other arm received enalapril. Analysis of the data indicated that enalapril was associated with a lower mortality rate than the combination of isosorbide dinitrate/hydralazine. However, a subsequent analysis comparing African American subjects and Caucasian subjects in the isosorbide dinitrate/hydralazine group indicated that African American subjects had substantial benefit from this therapy, while it was of little benefit to Caucasians.
These data subsequently were used by a pharmaceutical company to support an application to the FDA for approval of a isosorbide dinitrate/hydralazine combination pill. The FDA rejected approval of this combination for all heart failure patients, but approved it for treatment of heart failure in African Americans.
– What explanations have been put forward to explain observed differences in disease prevalence and outcome in individuals of different ethnic/racial backgrounds?

– Is it justified to use race or ethnicity subgrouping for analysis of clinical trial data?

– Some people argue that, even if there are genetic differences in response to treatment, use of race as a surrogate to identify such differences is unwarranted because it reinforces racist attitudes and does more harm than good. Do you agree or disagree? Are there ways to minimize the potential for adverse affects?
3. Mary O'Reilly is a 30 year old woman who decided to participate in a research study searching for genes causing inherited deafness. She has been deaf since early infancy but no information about her family history is known, as she was adopted.

Exome sequencing was performed on her DNA, along with 20 other deaf individuals. She and 2 other subjects were found to have nonsense mutations in a gene of previously unknown function. The gene is expressed in hair cells in the cochlea which leads the researchers to believe it is responsible for these subjects' deafness.

This information is provided to Mary and she is happy to finally know the cause of her deafness, though identification of the genetic mutation will not affect her hearing loss.
In analyzing her DNA sequence, the research team unexpectedly finds that Mary also carries a mutation in the BRCA1 gene. This mutation has previously been identified to be one of the most common BRCA1 mutations in women of Ashkenazi descent.

- Should the research team inform her of this finding?
- Should they tell her that, while raised Catholic in an Irish family, she is really of Jewish ancestry?
- What if the mutation, rather than being a known disease-causing mutation, is a previously undescribed missense “variant of unknown clinical significance”? 
4. A major medical center has decided to develop a biobank (tissue repository) so that researchers can have access to biopsy samples from patients who go to surgery because of a suspected or confirmed diagnosis of cancer. The head of the biobank proposes that, because 1) the samples will be left over material (discarded tissue) from clinically-indicated operations and 2) names and medical record numbers will be removed from the samples, it is not necessary to approach patients and obtain their consent for use of the tissue.

- Should the IRB grant a waiver and allow the samples to be used without consent?
- Should the researchers be allowed to review patient medical records to get information such as age at diagnosis, history of other cancers, presence of other medical conditions?
The cancer biobank proves to be very successful and the director decides that she would like to expand the scope so that samples are available for a broader range of research. She goes to the hospital administration and proposes collecting samples of all types (blood, urine, tissue from all surgeries) from every patient who is admitted to the hospital. As before, these will all be samples that are left over from clinically performed testing. In addition to reviewing the medical records for current medical information, she also proposes retaining a computerized link to the medical record, so that future medical information can be collected (such as the subsequent development of cancer, age of death) and linked to the samples. This link will also be used to connect samples collected during future hospitalizations to the original samples.
- Should the institution agree to expanding the biobank?
- What additional information would you need to have to decide if this is reasonable to do?
- Is consent from patients needed?
- Is informed consent feasible?
  - If yes, how?
5. Subjects have participated in a national, multicenter study to find the genes responsible for Type 2 (adult onset) diabetes. One of the goals of the study was to establish a cell line bank of EBV-transformed lymphoblastoid cell lines so that DNA can be given to many investigators involved in Type 2 diabetes research. The samples are coded and, when DNA is distributed, no direct identifiers are given out, but the national bank retains the link that matches the code with the original subject’s identity. Shortly after this cell line bank was established, the gene responsible for hemochromatosis was identified. Hemochromatosis is a disease of iron overload that can cause diabetes, cirrhosis of the liver, hepatic cancer, and cardiac failure.
An investigator who had requested and received samples from the bank was asked by a colleague whose lab was across the hall from hers if he could look for hemochromatosis mutations in the diabetes samples, since nobody had a clear idea of how often patients with hemochromatosis were misdiagnosed as having garden-variety type 2 diabetes. The first investigator gave the DNA to her colleague, thinking this was a good scientific question. A few months later, her colleague comes back, saying that he has identified 12 cases of hemochromatosis and wonders what they should do with the results. They draft a letter listing the ID numbers that were found to carry hemochromatosis mutations and send it to the tissue bank.
- What should be done with this information? Should the original subjects be notified? If so, how?
- Can the reliability of these findings be assured?
- What might be done to avoid problems in the future?