The Nuremberg Code

#1 "The voluntary consent of the human subject is absolutely essential."
Q: But what about children? Adults with cognitive impairments?
A: Vulnerable subpopulations!

The “Subpopulation” Approach

45 CFR 46: IRBs must consider “special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons”
The “Subpopulation” Approach

Is there something common to . . .
- Drug abusers?
- The desperately ill?
- Ugandan women?
- The impoverished homeless?
- Women in the throes of miscarrying?
- Psychology undergraduates?
- Military enlistees? Etc. . .

The “Subpopulation” Approach

Is there some distinctive feature that makes those who possess it “vulnerable”? If there is, what exactly should researchers do when they encounter a vulnerable candidate research subject (a CS)?

And why?

The “Subpopulation” Approach

A Regulatory Strategy?
Develop regulatory “subparts” for each vulnerable population?

A New Issue
What is meant by “vulnerable”?
How many subparts are we going to need?

Let's go back to the beginning . . .

. . . to Consent

Consent as an Ethical Power

- The power to turn a prohibited action into one that is permitted
  - A neighbor takes & uses your lawnmower
  - Rape
- But there are Misfires
  - Consent can fail to effect permissibility
  - I permit my neighbor to “borrow” your lawnmower: “It's OK with me!”
Consent as an Ethical Power

Many ways consent can misfire

- The science may be bogus
- The subjects may be unjustly selected
- The risks/burdens may be excessive
- There may be dangers to third parties or . . .
- Shortcomings among researchers, institutions, social settings, . . .
- Et cetera . . .

Vulnerability Defined

A condition of a candidate-subject (a CS) that calls into question the efficacy of consent in effecting the permissibility of proposed research

Notwithstanding consent, research may still be impermissible

Vulnerabilities

- Can impair the connection between “consent” and permissibility
- But these “impairments” can frequently be remedied by compensating measures
- Vulnerability: A cautionary signal rather than a flashing red light
An “Analytical” Approach

1. What are the species of “Vulnerability”
2. What are the different conditions that signal it?
   A “Taxonomy” of vulnerabilities
3. How should a vulnerable candidate research subject (a CS) be protected?
   Compensating Measures

Utility of this Approach

- A “Checklist” of circumstances that can invalidate the permissibility of research
- An intellectual basis for treating individuals as vulnerable
- A set of compensating measures that might effect permissibility
- A basis for warranted criticism

Background Concerns

- Precariousness in the subject, being laid open or especially exposed to something undesirable: an avenue of attack
- Others who are disposed to capitalize on weakness, exploiting avenues of attack, taking unfair advantage of a candidate research subject’s weakness
A Taxonomy of Vulnerabilities

1. Cognitive
2. Situational
3. Juridic
4. Deferential
5. Medical
6. Allocational
7. Social

1. Cognitive Vulnerability

**Question:** Does the CS have the capacity to deliberate about and decide whether or not to participate in the study?

2. Situational Vulnerability

**Question:** Can the CS be informed and complete effective deliberation within the therapeutic window?
3. **Juridic Vulnerability**

**Question:** Is the CS liable to the authority of others who may have an independent interest in that participation?

4. **Deferential Vulnerability**

**Question:** Is the CS given to patterns of deferential behavior that may mask an underlying unwillingness to participate?

5. **Medical Vulnerability**

**Question:** Has the CS been selected, in part, because he or she has a serious health-related condition for which there are no satisfactory remedies?
6. Allocational Vulnerability

**Question:** Is the CS seriously lacking in social goods that will be provided as a consequence of participation in research?

7. Social Vulnerability

**Question:** Does the CS belong to a socially undervalued group? [NBAC]

1. Cognitive Vulnerability

**Question:** Does the CS have the capacity to deliberate about and decide whether or not to participate in the study?

Compensating measures: Plain-language consent forms, advance directives, supplementary educational tools, surrogates and advocates, etc.
2. Situational Vulnerability

**Question:** Can the CS be informed and complete effective deliberation within the therapeutic window?

**Compensating measures:** Community consultation and notification, advance directives, bracelets (protections associated with the emergency exception to informed consent -- EFIC)

3. Juridic Vulnerability

**Question:** Is the CS liable to the authority of others who may have an independent interest in that participation?

**Compensating measures:** Confidentiality, exclusion of superordinates from accrual process, use/presence of ombudspersons.

4. Deferential Vulnerability

**Question:** Is the CS given to patterns of deferential behavior that may mask an underlying unwillingness to participate?

**Compensating measures:** Careful selection/training of accrual personnel, use of anthropologists and informants, attention to setting.
5. Medical Vulnerability

Question: Has the CS been selected, in part, because he or she has a serious health-related condition for which there are no satisfactory remedies?

Medical Vulnerability: The Worry

The Therapeutic Misconception: Despite warnings, subjects enter trials on the chance they will benefit from access to a drug that works. There is often no such chance

- Sub-therapeutic dosages
- Trial ends, leaving patients who were improving in the lurch

P1 Clinical Trial: Chemo
Medical Vulnerability

Patients should be assured that they WILL have a chance of benefiting from participation IF it turns out that the intervention is safe and effective.

A fairer division of the benefits and burdens of cooperation.

P1 Trial: Chemo - Modified

5. Medical Vulnerability

Question: Has the CS been selected, in part, because he or she has a serious health-related condition for which there are no satisfactory remedies?

Compensating measure: Design the trial to ensure the maximum probability of subject benefit.
6. Allocational Vulnerability

Question: Is the CS seriously lacking in social goods that will be provided as a consequence of participation in research?

Compensating measures: Look to the standards routinely applied to comparable and familiar remunerative activities. “Fair compensation”

7. Social Vulnerability

Question: Does the CS belong to a socially undervalued group? [NBAC]

Compensating measures: Involve members of the community in study design, review and implementation

Multiple Vulnerabilities

It is easy for a single subject to exhibit several forms of vulnerability. A third-world girl, suffering from an acute episode, could, for example, exhibit all seven.
General Recommendations

1. Move away from the "subpopulation" focus and towards an analytical model.
2. Studies on medically exigent patients should meet the "maximal therapeutic benefit" standard.
3. Give further attention to "fair compensation" for allocationally disadvantaged research subjects.

Final thoughts

Universality of Vulnerability

Kindness and Sensitivity

Acknowledgments

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Thank you

Request a copy of these slides at:

kkipnis@hawaii.edu
Assessing Risk in Vulnerable Populations

Disclaimer

The views and opinions expressed in this talk are my own. They do not represent the position or policy of the NIH, DHHS, or U.S. government

Risk Evaluation

- Clinical research is ethical only when it has important social value and the risks to subjects are acceptable.
- Hence, risk evaluation is central to ensuring ethical clinical research.
Belmont Report

- When deciding whether to approve a study “The nature, probability and magnitude of risk should be distinguished with as much clarity as possible.”

Components Analysis

- Research studies typically involve a number of interventions and procedures.
- Risk evaluation should consider the risks of the individual interventions, and the cumulative risks of the study as a whole.

Clinical Interventions

- Research studies often include standard clinical interventions.
- These interventions typically do not need to be evaluated for risks.
- **Caveat:** Research interventions can alter the risk-benefit profile of clinical interventions.
Research Interventions

- Risk evaluation should focus on the research interventions that subjects undergo.
- U.S. regulations: IRBs do not consider the risks of interventions subjects would undergo even if not participating in research.

Risk Evaluation

Step 1: Is each research intervention needed to collect important information?

Step 2: Are the risks of the interventions minimized?

Step 3: Are the risks of the interventions acceptable?

Step 4: Are the cumulative risks of the study acceptable?

Potential Benefit Research

- The risks of some research interventions are justified by their prospect of clinical benefit for subjects.
- The risks of these interventions are acceptable (step #3).
‘Non-beneficial’ Research

- Many research interventions do not offer a prospect of clinical benefit (which justifies their risks).
- Unclear whether there is/should be a limit on these risks for research with competent adults.

Vulnerable Subjects

- Non-beneficial research interventions typically may be approved in vulnerable subjects only when the risks are minimal.
- For example, U.S. regulations allow IRBs to approve pediatric research that does not offer a prospect of direct benefit only when the risks are minimal (or a minor increase over minimal in some cases).

Minimal Risk: Definition

“Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests”

(45CFR46)
Relevance

Determination that risks are ‘minimal’ has important implications, especially for vulnerable individuals:
- Healthy children and prisoners may be enrolled
- Informed consent may be waived
- Emergency research without consent allowed
- Full IRB review not necessary

Definition

- Minimal risks are risks that are not greater than the risks of daily activities or routine procedures.
- Hence, routine procedures used for research are, by definition, minimal risk.

Example

- A single blood draw is a routine procedure.
- Hence, a single blood draw used for research is minimal risk.
**Procedural Interpretation**

- Some might conclude that procedures which individuals do not ordinarily face in daily life are necessarily greater than minimal risk.

- Counterexample: Reiki

**Lesson**

- The regulations are designed to protect vulnerable subjects from excessive risks, not protect them from new experiences.

- Whether a research procedure poses minimal risk depends on the level of risk it poses for participating subjects.

**The Right Approach**

- Do the risks of the procedure exceed the level of risks individuals face from activities of daily life?

- Whose daily life?
Whose Daily Life?

- Enrolling individuals in riskier research because they happen to face greater risks in daily life (e.g. patients who undergo toxic chemotherapy) seem unethical.
- Most commentators define minimal risk as the risks “average, healthy, normal” individuals encounter in daily life.

IOM report on research with children

Caveat #1

- The risks of many activities (e.g. mountain climbing) are accepted because they offer personal benefit.
- The risks of these activities do not provide an appropriate standard for evaluating the ethical acceptability of non-beneficial research procedures and studies.

Caveat #2

- Daily life poses some risks to average, healthy, normal individuals that we regard as inappropriate, such as the risks of being abused.
- These risks also do not provide an appropriate standard for evaluating the ethical acceptability of non-beneficial research procedures and studies.
Charitable Participation Standard

- The minimal risk standard should be limited to risks in daily life that are *acceptable* for average individuals in the context of activities to benefit *others*.

- Examples: appropriate charitable activities, car trips for others, taking care of an infirm neighbor.

The Risk Threshold

- Acceptable ‘non-beneficial’ activities pose a range of risks: chatting with a sick neighbor is less risky than mowing their lawn.

- To qualify as ‘not greater than’ the risks of daily life, research risks must fall *within* this range.

- Test: do the research risks exceed the top of the range of risks of acceptable activities?

Minimal Risk?

- Allergy skin testing in healthy 11 year-olds
IRB Chairpersons’ Views
(N=188; response rate=84%)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Minimal Risk (MR)</th>
<th>Minor Inc over MR</th>
<th>&gt; Minor Inc over MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 cc Blood Draw</td>
<td>81%</td>
<td>17%</td>
<td>1%</td>
</tr>
<tr>
<td>MRI w/o sedation</td>
<td>48%</td>
<td>35%</td>
<td>9%</td>
</tr>
<tr>
<td>Allergy Skin Testing</td>
<td>23%</td>
<td>43%</td>
<td>27%</td>
</tr>
<tr>
<td>Lumbar Puncture</td>
<td>6%</td>
<td>32%</td>
<td>56%</td>
</tr>
</tbody>
</table>


Sources of Variation

- Why is there so much variation, and caution, in judgments of minimal risk?
- One possibility is that IRBs are reluctant to approve research in vulnerable subjects that does not offer a prospect of clinical benefit.

Response

- To address this reluctance, it is necessary to determine whether it is ethical to enroll vulnerable populations in non-beneficial research.

Judgment Without Data

- In addition, we often assume that we are familiar with the risks of daily life and rely on our intuition.
- Yet, psychological studies show individual risk perception is prone to systematic mistake; we focus on how familiar an activity is and our level of control over it.

The Need for Data

- Review committees should not assess the risks of clinical research using just their own personal intuitions.
- Instead, review committees need data on the risks of research procedures, the risks of daily life, and a way to compare them.

Risks of Everyday Life

- There are very few data on the risks of appropriate, 'non-beneficial' activities in daily life. Thus, there is a need to collect more and better data.
- Existing data bases provide some information, such as the risks of riding in a car.
The Comparison

- The minimal risk standard asks whether the level of risk posed by the research intervention exceeds the level of risk posed by appropriate activities in daily life.
- Making this assessment requires a method to compare the level of risk posed by research interventions to the level of risk posed by activities in daily life.

Bronchoscopy

- Research bronchoscopy involves insertion of a flexible tube into the airway, via the throat.
- Bronchoscopy poses a risk of airway abrasion: moderate discomfort for several hours with risk of minor bleeding.

The Options

- Is research bronchoscopy minimal risk or greater than minimal risk?
- There are at least 4 different comparisons we can use to answer this question.
#1 Routine Intervention
- Is the research intervention also used in daily life for average individuals?
- Measurements of weight are common procedures; bronchoscopy is not.
- It does not follow that bronchoscopy is necessarily more than minimal risk (remember Reiki).

#2 Same Risk
- Does an appropriate (non-beneficial) activity of daily life pose the same (or greater) risk as the research intervention?
- An ordinary flight involves exposure to the same level of radiation as a standard research X-ray (clinical records versus research records).
- No common activity in daily life poses the same likelihood of airway abrasion as bronchoscopy.

#3 Same Harm
- Does an appropriate activity of daily life pose a risk of the same harm as the intervention? If so, which is more likely?
- Likelihood of death in phase 1 study versus likelihood of death in ordinary car trip.
- Seems essentially no risk of airway abrasion in daily life (sword swallowers are not average!).
## #4 Different Harms

- How do we evaluate the risks of research interventions when the intervention is not used, and the harm is not posed, in daily life?

- How do we compare the risk of airway abrasion from bronchoscopy to the risk of harm from appropriate, non-beneficial activities in daily life (e.g., chance of broken arm on bike ride)?

## General Idea

- We need a systematic way of comparing harms of different types.

- Risk is a function of the magnitude of the possible harm (which itself is a function of the harms’ severity, duration, reversibility, impact on different interests), and the likelihood of experiencing that harm.

## Risk

- Determine the magnitude of the research harm and then see whether the likelihood of that harm exceeds the likelihood of experiencing a harm of the same magnitude during an appropriate, non-beneficial activity in daily life.

- Comparing likelihoods is easy, leaving the challenge of comparing the magnitudes of different types of harms.
Continuum Harms

- Harms occur on a continuum from minor bumps and boredom that setback one’s interests in avoiding discomfort to death and serious disability, which setback many or all of one’s interests.

- To make comparisons, it is useful to divide the continuum (somewhat arbitrarily) into categories.

Comparing Magnitudes

- To compare the magnitudes of different harms, we needed to develop a scale of magnitudes.

- The resulting 7 category scale was developed based on existing scales of harms to health, psychological data on the number of categories individuals can manipulate, and extensive consultation.

<table>
<thead>
<tr>
<th>Level</th>
<th>Example</th>
<th>Risk Daily Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negligible</td>
<td>Bruise</td>
<td>100K/100K</td>
</tr>
<tr>
<td>Minor</td>
<td>Common cold</td>
<td>22,000/100K</td>
</tr>
<tr>
<td>Moderate</td>
<td>Bone Fracture</td>
<td>7/100K</td>
</tr>
<tr>
<td>Significant</td>
<td>Knee instability</td>
<td>8/100K</td>
</tr>
<tr>
<td>Major</td>
<td>Rheumatoid Arthritis</td>
<td>0.008/100K</td>
</tr>
<tr>
<td>Severe</td>
<td>Paraplegia</td>
<td>0.03/100K</td>
</tr>
<tr>
<td>Catastrophic</td>
<td>Death</td>
<td>0.2/100K</td>
</tr>
</tbody>
</table>
Systematic Evaluation Research Risks

1. Identify potential harms of intervention;
2. Categorize magnitude of potential harms;
3. Quantify likelihood of potential harms;
4. Compare likelihood of each potential harm from intervention to the likelihood of harm of the same magnitude from daily life.

Rid, Emanuel, Wendler. *JAMA* 2010; 304:1472-1479

Summary

- Evaluation of research risks is vital to ensuring ethical research, especially in vulnerable populations
- Typically, risks should be minimal (for all vulnerable groups?)
- Intuitive judgment of risks is unreliable
- We need to collect data on risks
- We need to develop systematic methods for evaluating risks
Considering and Developing Additional Protections for Vulnerable Participants: The Regulatory Mandate

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April 20, 2012
[Disclaimer]

Vulnerable Participants by Subpart

Vulnerable Participants by Subpart
(almost)
Vulnerable Participants by Mention

Vulnerable Participants by Type of Protection (1)

“If an IRB regularly reviews research that involves a vulnerable category of subjects, such as [a list]…consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.”(.107(a))

Vulnerable Participants by Type of Protection (2)

• “Selection of subjects is equitable. …the IRB should be particularly cognizant of the special problems of research involving vulnerable populations, such as…[ a list].”(.111(a)(3))
Vulnerable Participants by Type of Protection (3)

“When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as [a list], additional safeguards have been included in the study to protect the rights and welfare of these subjects.” (.111(b))

Vulnerable Participants by Type of Protection (4)

• Specific Subparts with various conditions, and with permissible and prohibited categories of research involving
  o Pregnant Women, Human Fetuses and Neonates
  o Prisoners
  o Children

Vulnerable Participants in History
Vulnerable Participants of the Day

Vulnerable Participants by Agency

- Variable adoption of Subparts B, C, and D.
- Special provisions, e.g.
  - VA policy on research-related injury
  - HIPAA and FERPA regulations on records
  - PPRA statute on student surveys
  - ED policy on IRB membership

A Case Study in Regulatory Developments Related to Vulnerable Participants in Research

The U.S. Department of Education and the Adoption of the Common Rule
Resistance to the Adoption of the Common Rule from Education (1985)

- 10 Departures strengthening protections for mentally disabled subjects in research
- 1 Departure not applying the Common Rule to activities covered by the General Education Provisions Act

IRB members & Vulnerable Subjects

“If an IRB regularly reviews research that involves a vulnerable category of subjects, including but not limited to subjects covered by other subparts of this part, the IRB shall include one or more individuals who are primarily concerned with the welfare of these subjects.”

(HHS regulation 107, 1981)

IRB members & Vulnerable Subjects

“If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.”

(OSTP Model Federal Policy, 1986)
IRB members & Vulnerable Subjects

“When an IRB reviews research that deals with handicapped children or mentally disabled persons, the IRB shall include at least one person primarily concerned with the welfare of the subjects”. (ED Departure, 1988)

IRB members & Vulnerable Subjects

“If an IRB regularly reviews research that involves a vulnerable category of subjects, such as [a list]…consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.” (Common Rule,.107(a), 1991.)

IRB members & Vulnerable Subjects

• “When an IRB reviews research that purposefully requires inclusion of handicapped children or mentally disabled persons as research subjects, the IRB must include at least one person primarily concerned with the welfare of these research subjects.” [Common Rule provision also included.] (NIDRR regulation, 350.3(d)(2))
The Advance Notice of Proposed Rulemaking (ANPRM)  
July 26, 2011  
Human Subjects Research Protections:  
Enhancing Protections for Research Subjects  
and Reducing Burden, Delay, and Ambiguity  
for Investigators

Vulnerable Subjects in the  
ANPRM?  
Subparts B, C, and D will need to be revised accordingly.  
No changes are proposed for Subpart A provisions specifically related to research involving vulnerable populations.  
No questions are asked specifically related to research involving vulnerable populations.

Why?  
• Revising Subpart A is more fundamental, logically prior, and complicated enough.  
• Regulations set the minimal requirements for research involving vulnerable populations.  
• The U.S.A. is a liberal democracy.  
• Research involving vulnerable populations elicits rival views of fairness.
The Vulnerability of the Regulatory Mandate

"No, I didn't. We've only had government regulation..."
Genetic Research: Is Everyone Vulnerable?

Objectives

- Review the conflict between utility of biological information and informational privacy
- Discuss the risks to individual identification based on genetic information
- Discuss protective measures to reduce risks to privacy and risks of stigma and discrimination
Is Privacy Obsolete in the Age of Genomics?

What are the risks to human subjects when genetic research is conducted on human tissues?

What is Privacy?
- Confidentiality: Protecting sensitive information disclosed within a professional relationship
- Privacy (ref Anita Allen)
  - Informational (concerns about access to personal information)
  - Physical
  - Decisional
  - Proprietary
What are the risks to human subjects when genetic research is conducted on human tissues?

- Discussion will focus on informational risks associated with the generation of genetic information from human tissues.
- Will not focus on issues arising in specific clinical research contexts:
  - Prenatal diagnosis
  - Genetic testing for cancer susceptibility
  - Gene transfer studies
  - Cloning….

Genetic Research Goals

- To better understand the relationship between genotype (a person’s genetic makeup) and phenotype (a person’s experience of health or illness)
- The more genotype and phenotype information, the better
- Tissues are essentially useless without phenotype information

Balancing Considerations
Regulatory Definitions in US

- When is research with tissues “human subjects research”?
  - *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
    - (1) Data through intervention or interaction with the individual, or
    - (2) Identifiable private information
  - The individual must *readily identifiable* to investigators under 45CFR46
  - Research with de-identified samples is not human subjects research (human non-subject research)

Privacy Standards in Research

- HIPAA de-identification standard
  - “A person with appropriate knowledge of and experience with generally accepted statistical and scientific principles … determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual …;” or
  - the removal of 18 potential identifiers, including names, addresses, social security numbers, account numbers, etc.

Privacy Standards in Research

- Risk of re-identification must be low, but not zero to be considered human non-subject research
- Other accepted practices in research entail a risk of identifiability
  - Publication of pedigrees
  - Case reports
Traditional Privacy Standards

OHRP 2004 Guidance

- Investigator A obtains tissues from research participants and retains a link to individual identifiers
- Investigator A shares tissues with Investigator B.
- Investigator B cannot determine the identity of the tissue sources but they remain "linked"
- If Investigator B agrees not to attempt to identify the identities of the tissue sources,
  - Then research by Investigator B is NOT human subjects research
  - No stipulation that agreements are under IRB oversight

The Role of Informed Consent
Ethical Issues

- Biobanks and data repositories permit the analysis of tissues/data in times and places remote from the source.
- How much control should sources have over research conducted with their samples/data?
- When is notification or consent required?
- What should be the scope and nature of informed consent?
- How should biobanks/databanks be governed in order to secure public trust?

Research Acquired Tissues

- How broad can the authorization be for future research use?
  - "Common rule" permits authorization for unspecified future use
  - HIPAA requires that the specific nature of the research be described
    - Unclear whether, say, "cancer research" is specific enough

Informed Consent and Secondary Research

- Often not required for secondary research on biobanked tissues
  - Human non-subjects research
  - Waiver of consent in human subjects research
- Obtaining informed consent is not the exclusive answer for managing risk to privacy
Individual Choice

- Informed consent functions poorly when:
  1. the research is conducted remotely from the tissue source, and
  2. the research involves analyses that were not anticipated at the time of acquisition

What are the Harms We are Concerned About?

- What are the risks to biobank and data repository – based research?
  - Breach of confidentiality or privacy => stigma/discrimination
  - Psychological impact to the participant from predictive information
- Such breaches are rare
- Limited psychological impacts
- Some protective measures in place for genetic information
  - Genetic Information Non-discrimination Act (GINA)
Group Harms and Wrongs

- 1989 study of type I diabetes was conducted at Arizona State University
- Havasupai Indians recruited and 400 clinical histories, family histories, and blood samples obtained
- Late 1990’s, discovered that research was conducted on schizophrenia and population migration studies using study materials
  – Allegedly without adequate consent for the secondary research

Public Attitudes

  – sample of adult patients at general medical, thoracic surgery, or medical oncology clinics
  – N= 1,193 (response rate 86%)
  – 81% wanted notification if identifiable tissues used in research
  – 72% wanted notification if anonymous tissues used in research
  • For those wanting notification, 56% want to give prior permission even for anonymous samples

Public Attitudes

- Hudson et al AJPH 2009:99:2128
  – National US survey of 4659 participants about biobank research
  – 48% supported blanket consent for future research
  – 42% wanted consent for each project using their sample
  – 10% wanted categorical consent (choices for types of research that might be conducted)
Public Concern about Privacy

- IOM Summary of Survey Data (Feb 2009)
  - Patients are generally supportive of research as long as safeguards for privacy are in place
  - Patients are much more comfortable with anonymized data use in research
  - Patients are less comfortable with data sharing about sensitive conditions
  - The majority of patients want to be consulted before information is released for research

Genetic Information

- Why might genetic information pose a unique threat to privacy?
- Genetic information can be uniquely identifying
  - DNA sequence information
  - Pedigree structures
- Genetic information can provide information about health status

Genomic Variation

- Unrelated persons differ in about 0.1% of their 3.2 billion base pairs in DNA
- Forensic identifications rely on 13 - 15 locations in the genome with variable repeats
- Analysis of 30 - 80 SNPs (single nucleotide polymorphism) can uniquely identify any individual
Genetic information vs. Privacy

- Insufficient for future genomic research
- Needed to find genetic relationships
- Insufficient for privacy protection

Trade-offs between SNPs and privacy.


DNA Sequencing

- Sequencing genomes
  - James Watson -- $2 million for full sequence
  - Goal => $1000 sequence

February, 1953

How revealing of private information is genetic information per se?

May, 2007
Genetic Determinants of Obesity

Researchers Discover New Genetic Risk Factors Involved in Adult and Childhood Obesity

Comprehensive Study Uncovers Six Genetic Variants Associated With Body Mass Index

http://www.genome.gov/27529231

December 2008

Botkin 2012

Obesity Study

- 32,000 individuals of European ancestry
- 15 genome-wide association studies identified and analyzed
- 35 genetic variants identified that are associated with BMI
- Results:
  - The 1% of the population with the most obesity-causing variants estimated to be 10 lbs. heavier than the 1% with the least number of variants

Implications to Date

- Aside from a relatively small number of Mendelian traits, genetic information is not proving to be highly predictive of health or physical status
- The threat from privacy breaches in genetics is proportional to the power of genetic information to give us meaningful information about the individual
- Sequence data per se is unlikely to produce stigmatizing information
Key Concern

- But, identification of a biospecimen may provide information about the individual from the linked phenotype data
- Can sequence data be anonymized?

What are the risks of identification?

- “… [T]he potential for identifying one’s individual sequence or that of someone else on a public database and finding known or suspected variants within it will be increasingly within the reach of the lay public, including employers, insurers, family members and other potentially interested parties.”

Matching DNA sequence information
Reality Check

- Reference database with sequence data and identifiers necessary to re-identify anonymous sequence on the internet
  - Most existing reference databases (military, forensic) are not publicly available
  - Online genealogical sites
    - Sorenson Family Tree DNA
    - Uses Y-Chromosome testing
    - But: Test data only released with consent
    - 3rd parties do not have access to individual test result information

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Reality Check

- Technology, expertise, and motivation required to match sequence information
  - Obtaining and interpreting sequence information is highly technical requiring substantial expertise
- Investigators have no motivation to identify de-identified biospecimens (no $ involved)

Botkin 2012

Reality Check

- Sequence must be sufficient to provide meaningful information about health status
  - Most of us do not have single gene disorders
  - Those with single gene disorders would need to have relevant sequence information available
- Risk information must be relayed to someone in a position to harm the source individual
  - Is the breach of privacy a harm independent of injury?
- To date, probability of insurance or employment discrimination based on genetic risk information is extremely low
  - Genetic Information Nondiscrimination Act (GINA)

Botkin 2012
What measures are being taken?

- Sequestering identifiers (reversible de-identifying sequence information)
- Limiting potentially identifying data associated with sequence information
- Providing access under conditional agreements
- Assurances from investigators that they will not attempt re-identification

Lowrance & Collins Science 2007;317:600

Conclusions

- Risk of identifying sources of raw DNA sequence data is very low
- Risk of harm associated with identification of sequence is extremely low
- The concept of “anonymous” is not obsolete relevant to sequence data and should be used
- Genetic privacy fears may unnecessarily inhibit research

OHRP Advance Notice of Proposed Rulemaking

- Issued in August, 2011
- Proposed changes in human subject regulations
  - All data and tissue repositories would be subject to HIPAA style privacy regulations
  - All tissues prospectively acquired in clinical care would require written informed consent for use in research
  - Consent could broadly cover future, unspecified research
  - Use of specimens under these conditions, whether identifiable or not, would not be subject to IRB oversight
Conclusions

- Alarm secondary to the privacy of sequence data on the internet reflects elements of
  - Genetic determinism
  - Genetic exceptionalism
- Excessive alarm over privacy of genetic information promotes fear, shame, stigma, and discrimination
- We should work to destigmatize genetic information, not build walls around data