Unique Human Subjects Concerns for Genetic Research

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Agenda / objectives for this session

Differentiate various types of genetic research
- Gene identification
- Genetic therapies (not our major focus today)

Discuss human subjects concerns unique to various types of genetic research
- Nature of discovered information
- Risks to privacy
Genetic Research Today
(a brief recap of Dr. Fong’s session)
Shift of focus from specific mutation associated with a rare disease to pattern of more common variations (genetic signature) associated with more common conditions
Possible because entire human genome has been sequenced: alternate versions of single nucleotides (SNPs) have been identified (3 million, of which 150,000 are in coding areas of chromosomes)
Genetic Research Today
(a brief recap of Dr. Fong’s session)
Inherited mutations are commonly identified by studying families with affected and unaffected members.

Genetic signature studies require very large databases of DNA and clinical information. The number of SNPs studied often exceeds the number needed to identify each human uniquely.
Types of Genetic Research

Gene identification

- **Known diagnosis*, unknown gene**
  - “association” studies
  - Involve subjects with and without the diagnosis who share other genes (e.g. family, common ethnicity)
  - Goal is identification of variants in gene or section of chromosome more common among those with diagnosis than those without diagnosis

* (or prognosis or response to specific therapy: may be secondary aim in drug trial)
Types of Genetic Research

Gene identification

- **Known diagnosis, unknown gene**, cont.
  - Scientific complications
    - Multiple genes involved in causing target disease
    - Not all persons with gene affected to same degree
  - Therefore, significance of having the “disease-associated” version of the gene is unknown, in terms of future health of individual and his/her offspring
Types of Genetic Research

Gene identification – Genome Wide Association Study (GWAS)

- **Known diagnosis, unknown genetic signature**
  - Diagnoses more commonly occurring, e.g. heart disease, asthma
  - May involve surveys of thousands of SNPs
  - Don’t depend on family or ethnic genetic similarities to detect relevant patterns
Types of Genetic Research

Gene identification – Genome Wide Association Study (GWAS)

- Known diagnosis, unknown genetic signature

- Require very large databases. Efficient to share these databases, since the sample genomes only have to be sequenced once to answer many clinical questions:
  - Mechanisms of pathology
  - Differences in prognosis
  - Differences in drug response
Types of Genetic Research

Genetic identification

- Known gene, unrecognized diagnosis
- “Genetic testing”
  - Individual
  - Family
  - Population (may serve study objectives other than biomedical, e.g. migration studies)
  - Identification of the gene variation in an individual or family provides previously unknown / unknowable information about future health
Types of Genetic Research

Genetic expression

- **Known diagnosis, known gene**
  - Goal of study is determining what genes are “turned on” or “turned off” in different diseases or situations
  - Does not focus on gene variations
  - RNA (single strand “messenger” produced by DNA) or proteins are indicators of gene activity
Types of Genetic Research

“Procedural” Genotyping

– Typically: known gene, known diagnosis
– Determine whether potential subject meets inclusion criteria for study
– Stratify outcome data for analysis
Types of Genetic Research

– Gene Therapy

• Vector (often virus) used to introduce functional gene variation into cells that have non-functional (disease-causing) variant
  – Severe combined immune deficiency ("bubble baby" syndrome)

• Cells genetically modified for specific purpose
  – T-cells modified to attack specific tumors

• Abnormal genes exchanged for normal genes or repaired

• Expression of gene altered (gene turned on or off)
Types of Genetic Research

–Gene Therapy, cont.

• Somatic cell – change what was inherited from past generations in an individual
• Germ cell – change what will be inherited by future generations
Unique Ethical Issues

Gene identification – Known diagnosis, unknown gene

- Clinical relevance of findings unknown
  - Diagnosis already established
  - Future implications of genetic analysis unknown
  - Should results be available to subject
    - Now?
    - In future? Under what circumstances?
Unique Ethical Issues

Gene identification – Known diagnosis, unknown gene

- Risk from incidental findings
  - Family analyses indicate no biological relationship where one is believed to exist
  - Genetic variants known to be associated with other diseases (not object of research) identified

- Family coercion for members (both affected and unaffected) to participate in research
Unique Ethical Issues

**Gene identification – Known diagnosis, unknown gene**

- Clinical relevance of findings unknown, cont.
  - Risks and benefits of removing identification from data
    - Assures confidentiality (at least until identifiable DNA banks become widespread)
    - Cannot contact subject about further research or obtain additional data
    - Cannot remove sample from further storage, use at subject request
Gene Identification – Descriptors for Stored Samples  Source: ICH E15

**Identified** data and samples – Identifiers stored with samples.

- Security equivalent to medical records
- Allows follow-up, return of samples and results, clinical use of results
- Insufficient security for drug trials
Gene Identification – Descriptors for Stored Samples  

Source: ICH E15

**Single coded** data and samples – No identifiers stored with samples, but investigator retains key between identifiers and code on samples.

- Allows follow-up, return of samples and results, clinical use of results
- Minimal acceptable security for drug trials
Gene Identification – Descriptors for Stored Samples  Source:  ICH E15

**Double coded** data and samples – No identifiers stored with samples, and code on samples connects to a coded key retained by the investigator. Second key, maintained elsewhere, links first code to identifiers.

- Allows follow-up, return of samples and results, clinical use of results
- Additional security because two code-holders must cooperate to link sample and subject.
Gene Identification – Descriptors for Stored Samples  Source: ICH E15

**Anonymised** samples and data – Initially single- or double-coded, but the keys linking the codes have been destroyed.

- Follow-up, return of samples and results, clinical use of results is no longer possible.
- Additional privacy protection, because subject identity can no longer be discovered via the key.
- Equivalent, once done, of HIPAA deidentification.
Anonymous samples and data – Identifiers never collected or labeled in the data.

- Follow-up, return of samples and results, clinical use of results is never possible.
- Lowest risk to privacy, because identifying information never available to investigators.
- As whole genome genotyping becomes more widespread, researchers will be able to reidentify even “anonymous” samples
Unique Ethical Issues

Gene identification – Known gene, unrecognized diagnosis

- What is risk to subject from the findings?
  - Personal awareness of future health threat
  - Possible discrimination in employment or insurance eligibility
  - Social implications

- How do we make sure subjects understand those risks, both prior to study participation and when results become available?

- How do we minimize the risks of disclosure?
Unique Ethical Issues

Gene identification – Known gene, unrecognized diagnosis

- Should children be enrolled / tested?
  - Would early detection improve outcome? (e.g. long QT syndrome)
  - Do potential benefits outweigh future adult’s right to make his/her own decision?
- What is risk to subject’s family from the findings?
  - Identify likely genetic status of non-participants from inheritance patterns
  - Social stigma
Unique Ethical Issues

Gene identification – Known gene, unrecognized diagnosis

– What is risk to *population* from the findings?
  • Social stigma
    – Stereotyping of minority population
    – Challenge to cherished cultural beliefs (e.g. Havasupi Indians)
– Research programs can transform from gene association to genetic testing when unknown genes are successfully identified
Laws Governing Known Gene, Unknown Diagnosis ("Genetic Testing")

NYS Civil Rights Law 79-1 and amendment

Federal Genetic Information Non-discrimination Act (GINA)
NYS Civil Rights Law 79-1 & Amendment

Definitions
(a) "genetic test" shall mean any laboratory test of human DNA, chromosomes, genes, or gene products to diagnose the presence of a genetic variation linked to a predisposition to a genetic disease or disability in the individual or the individual`'s offspring; such term shall also include DNA profile analysis. "Genetic test" shall not be deemed to include any test of blood or other medically prescribed test in routine use that has been or may be hereafter found to be associated with a genetic variation, unless conducted purposely to identify such genetic variation.
Definitions

(b) "genetic predisposition" shall mean the presence of a variation in the composition of the genes of an individual or an individual`s family member which is scientifically or medically identifiable and which is determined to be associated with an increased statistical risk of being expressed as either a physical or mental disease or disability in the individual or having offspring with a genetically influenced disease, but which has not resulted in any symptoms of such disease or disorder.
NYS Civil Rights Law 79-1 & Amendment

2. (a) No person shall perform a genetic test on a biological sample taken from an individual without the prior written informed consent of such individual. (b) Written informed consent to a genetic test shall consist of written authorization that is dated and signed and includes at least the following: (1) a general description of the test; (2) a statement of the purpose of the test; 2-a. a statement indicating that the individual may wish to obtain professional genetic counseling prior to signing the informed consent. (3) a statement that a positive test result is an indication that the individual may be predisposed to or have the specific ...(4) a general description of each specific disease or condition tested for; (5) the level of certainty that a positive test result for that disease or condition serves as a predictor of such disease......
A general waiver, wherein consent is secured for genetic testing without compliance with paragraph (b) [previous slide] of this subdivision, shall not constitute informed consent. [That’s why subjects may need to be recontacted for subsequent genetic testing of their specimens, but ......]

For medical research purposes, with the approval of an institutional review board and the written informed consent of the subject, samples may be kept for longer than sixty days and utilized for scientific research. The requirements of subparagraphs three, four and five of paragraph (b) of this subdivision [specificity of disease and accuracy of the test] may be modified by the institutional review board in case the research protocol does not permit such degree of specificity.
NYS Civil Rights Law 79-1 & Amendment

(a) Notwithstanding the provisions of subdivision two of this section, genetic tests may be performed on anonymous samples for research or statistical purposes, pursuant to a research protocol approved by an institutional review board which assures the anonymity of the sources of the samples.
9. (a) Notwithstanding the provisions of subdivisions two and ten of this section, samples may be used for tests other than those for which specific consent has been obtained, for purposes of research conducted in accordance with applicable law and regulation and pursuant to a research protocol approved by an institutional review board, provided that the individuals who provided the samples have given prior written informed consent for the use of their sample for general research purposes and did not specify time limits or other factors that would restrict use of the sample for the test, and (1) the samples have been permanently stripped of identifying information; or (2) a coding system has been established to protect the identity of the individuals who provided the samples, and an institutional review board has reviewed and approved the procedures for the coding system.
Unique Human Subjects Issues

The dilemma:
Given current genetic testing capabilities, even an anonymous specimen carries the identification equivalent of a fingerprint (the pattern of SNPs). Protection of privacy requires control of access to DNA banks with linked identifiers (military, criminal justice, research).

In the near future, researchers may be able to infer sex, age, race and health information from an anonymous sample to recreate traditional identifiers without reference to an identified DNA bank.

How much should privacy matter? Who gets to decide? Who should be responsible for protecting it?
Genetic Information Non-discrimination Act of 2008 (plus prior HIPAA)

Prohibits health insurers from requesting, requiring or using genetic information for decisions about coverage, rates or pre-existing conditions. (Does NOT apply to life insurance, disability insurance or long-term care insurance.)

Prohibits most employers from using genetic information to make hiring, firing and promotion decisions, or any decisions about terms of employment.
Genetic Information Non-discrimination Act of 2008 (plus prior HIPAA)

**Genetic information is defined as:**
Genetic tests on individual (including those done for research): analysis of DNA, RNA, chromosomes, proteins or metabolites to detect genotypes, mutations, or chromosomal changes
Genetic tests on individual’s family members
Fetal genetic testing
Family history of inherited disorders
Participation in genetic services or research involving genetic services by individual or family member
Genetic Testing – Informed Consent Components

Source: Dartmouth Committee for the Protection of Human Subjects

What information about their results subjects will receive and when
Possibility of finding out things they do not really want to know
Possibility of their families learning information about subjects
Whether release of study findings could affect their insurability
Genetic Testing – Informed Consent Components

Source: Dartmouth Committee for the Protection of Human Subjects

Risks of taking part in study activities (e.g. insurance company receiving bill for genetic counseling)

Rights (or not) to further control of study specimens, once donated

Consequences of withdrawing from study

Costs associated with taking part in study, if not covered by study (e.g. counseling)

Limits to study ability to keep results confidential
Unique Ethical Issues

**Gene Expression Studies**
No unique issues - Results unlikely to provide immediate clinical benefit or cause harm to study subjects

Privacy issues for further research on retained specimens apply here, too
Unique Ethical Issues

**Gene Therapy Studies**

Safety of the vector used to insert

- Immune, inflammatory responses (Jesse Geisinger)
- Control and targeting
  - Spread to non-targeted cells
    - Disable tumor suppression cells
    - Spread to germ cells
Unique Ethical Issues

Gene Therapy
Defining what genes need to be “fixed”
- Severe combined immune deficiency?
- Complete color blindness?
- Male pattern baldness?
- Are disabilities diseases to be “cured”?  
Somatic vs. germ cell therapies
- Is it ethical to alter genes to be passed on for research purposes to a generation that cannot consent to be in the research?
- Current consensus is NO
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