PREP #15:
Genetic Testing in Human Subjects Research

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CME Disclosure Statement

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• Course Director and Course Planner, Kevin Tracey, MD and Tina Chuck, MPH have nothing to disclose.

• Richard D. Ramdeo has nothing to disclose.
Objectives

Discuss the regulatory and ethical framework for the return of genetic testing when conducting Human Subjects Research.

Topics:

• Define genetic testing and explain the aspects in which it can be used in Human Subjects Research.
• Outline the regulatory & ethical framework when considering the return of genetic results to symptomatic and asymptomatic subjects.
• Describe the lab qualifications needed when considering the return of genetic results.
• Provide an outline of the consent requirements and discuss considerations when returning results to the participant and/or physician.
• Discuss the return of genetic results from incidental findings.
• Discuss case studies.
What is genetic testing?

Genetics is the study of heredity, which is the process in which traits and characteristics are passed to offspring by parents. The ‘instructions’ for these traits and characteristics are held within the body’s cells as a gene.

• These genes are vital in determining how an individual behaves and functions. They can determine physical traits such as hair color as well as determine the likelihood of getting a disease or disorder.

Genetic testing covers an array of techniques to analyze DNA, RNA, and/or proteins. Genetic tests are used as a health care tool to detect gene variants associated with a specific disease or condition, as well as for non-clinical uses such as paternity testing and forensics.
Types of Genetic Testing

1. **Diagnostic testing** is used to identify the disease that is making a person ill. The results may help make disease treatment and management choices.

2. **Predictive and pre-symptomatic tests** are used to find gene changes that increase a person's likelihood of developing diseases. The results of these tests provide information about the risk of developing a specific disease.

3. **Carrier testing** is used to find people who "carry" a gene that is linked to disease, while not actually having the disease itself.

4. **Prenatal testing** is offered during pregnancy to help identify fetuses that have certain diseases.

5. **Newborn screening** is used to test babies after birth to find out if they have certain diseases known to cause problems with health and development.

6. **Pharmacogenomic testing** gives information about how certain medicines are processed by an individual's body. This type of testing helps healthcare providers choose the best medicine(s) based on genetic makeup.

7. **Research genetic testing** is used to learn more about the contributions of genes to health and to disease.
Research is a *systematic investigation, designed to develop or contribute to generalizable knowledge*.

**Human Subjects Research** is research in which:

- An investigator obtains information about a living individual through intervention or interaction,
- An investigator obtains private and identifiable information about a living individual, or
- An individual will be a recipient of a test article (drug or device), serve as a study control, or have a medical device used on their specimen.
Genetic Tests as Medical Devices

Genetic tests are generally considered a medical device.

A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent, or other similar article, including any part or accessory, that is:

- recognized by official FDA appointed compendia such as the National Formulary or the United States Pharmacopoeia,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or
- intended to affect the structure or function of the body without the use of direct chemical reactions or being metabolized.
The ‘Traditional” Medical Device:
• a machine or instrument intended for use in the diagnosis of a disease

Biological Staining:
• Dye and chemical solution stains are mixtures of dyes or non-dye chemicals in solutions used in staining cells and tissues for diagnostic purposes.
• Immunohistochemistry reagents and kits are in vitro diagnostic devices consisting of antibodies where the intended use is to identify, by immunological techniques, antigens in tissues or cytologic specimens.
• Early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) is a device intended to detect the EGR1 probe target on chromosome 5q in bone marrow specimens from patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).
  • Usually incorporates comparative genomic hybridization (analysis of copy number variations in the DNA) and Banding (staining technique to identify number and appearance of chromosomes).
Research involving genetic tests that are considered a medical device undergo expedited IRB review if it involves:

1. A legally marketed device used in accordance with its approved labeling.
2. Research where the device is used as a tool to obtain information or investigate a basic physiological principle.
3. A non-invasive diagnostic device that does not require invasive sampling procedures that presents significant risk, does not introduce energy into a subject, and is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.
Research involving genetic tests that are considered a medical device undergo full board IRB review if it involves:

1. An unapproved device or an approved device being used in an unapproved manner, and is not otherwise exempted from this requirement.
2. A device considered the subject of a research study and is not otherwise exempted from this requirement.
3. A device that presents the potential for serious risk of harm.
4. A device that may substantially impact clinical care.
Regulations and Genetic Testing

Food and Drug Administration:
• Commercial Marketing: Regulates the test as a medical device.
• Laboratory-developed Testing (LDT): Exercises enforcement discretion. However, will expand its oversight of LTDs since they are more commonly being used in clinical decisions such as determining the best drug.

Centers for Medicare and Medicaid Services:
• Regulates the laboratories performing genetic testing through Clinical Laboratory Improvement Amendments (CLIA). The objective of CLIA is to certify the clinical testing quality, including verification of the procedures used and the qualifications of the technicians processing the tests.

Federal Trade Commission:
• Regulates advertisement claims.
New York State Civil Rights Law (Section 79-I):

- The law was enacted to protect the privacy of genetic information, restricting the disclosure of results, and placing limitations and requirements for informed consent.

- The New York Law has a specific and limited definition of Genetic Test. It only applies to tests conducted to learn whether an asymptomatic person (not producing or showing symptoms) has a genetic predisposition to a disease or disorder. It does not apply to:
  1. Tests performed on a person with symptoms of the disease or disorder;
  2. Tests performed for the purpose of answering a research question, where the ultimate purpose of performing the test is not to identify a genetic variation. An example of such a test would be a test to gauge the efficiency of a diagnostic test by comparing it to another test.
New York State Civil Rights Law

If the activity involves a genetic test as per New York State Law, the activity is classified as one of the following:

1. Genetic Tests performed for research purposes on pre-existing anonymous or de-identified samples.

2. Genetic Tests performed for research purposes only.

3. Genetic Tests performed, at least in part, for clinical purposes.
Genetic Tests performed for research purposes on pre-existing anonymous samples:

- Section 79-I does not require informed consent for Genetic Tests performed on pre-existing anonymous samples, for which there is no identifiable person from whom to obtain consent, provided that the IRB determines that the research protocol assures the anonymity of the sources of the samples.
New York State Civil Rights Law

Genetic Tests performed for research purposes only:

Genetic Tests may be performed on samples for research purposes if:
• the individual providing the sample gave prior written informed consent for the use of their samples for the general research purpose, and
• the samples have been permanently stripped of identifying information or an IRB-approved coding system has been established to protect the identity of the individuals that provided the samples.

If the study contemplates on communicating the test results to the individual or their physician, the activity is considered a “Genetic Test performed, at least in part, for clinical purposes” and must abide by its requirements.

Keep in mind that with testing performed for research purposes only, there is no requirement to disclose the results to the participant. The IRB would not require its disclosure just as long as the consent states that results won’t be disclosed.
New York State Civil Rights Law

Genetic Tests performed for research purposes only:

Written informed consent must include the following:

• statement that the sample will be used for future Genetic Tests;
• the time period during which the sample will be stored (if no time limit is specified, a statement that the sample will be stored for as long as deemed useful for research purposes);
• a description of the policies and procedures to protect patient confidentiality;
• a statement of the right to withdraw consent to future use of the sample, and the information of who to contact to be withdrawn;
• a statement allowing individuals to consent to future contact for any or all purposes, including the following: (i) research purposes; (ii) provision of general information about research findings; and (iii) information about the test on their sample that may benefit them or their family members in relation to their choices regarding preventative or clinical care; and
• a statement explaining the benefits and risks of consenting to future contact.
New York State Civil Rights Law

Genetic Tests performed, at least in part, for clinical purposes:

A genetic test is considered a *clinical* genetic test if:

• The results are to be communicated to the research participant or the participant’s doctor,
• The participant’s family members will be contacted in relation to the test results,
• The results will be linked to the participant’s identity and disclosed to any organization or other person, or
• The results will have significant importance to treatment.
New York State Civil Rights Law

Genetic Tests performed, at least in part, for clinical purposes:

Written informed consent must include the following:

• a general description of the test;
• a statement of the purpose of the test;
• a statement indicating that the individual may wish to obtain professional genetic counseling prior to signing the informed consent;
• the name of the person or categories of persons/organizations that may receive results;
• * a statement that a positive test result is an indication that the individual may be predisposed to or have the specific disease or condition tested for and may wish to consider further independent testing, consult their physician, or pursue genetic counseling;
• * a general description of each specific disease or condition tested for;
• * the level of certainty that a positive result for that disease or condition serves as a predictor of such disease (not applicable if no level of certainty has been established);
• a statement that no tests other than those authorized shall be performed on the biological sample and that the sample shall be destroyed within sixty days after the sample was taken, unless a longer period of retention is expressly authorized in the consent; and
• the signature of the individual subject of the test, or if that individual lacks the capacity to consent, the signature of the person authorized to consent for such individual.
Additional Consent Suggestions

National Center for Biotechnology Information (NCBI) has created a database of Genotypes and Phenotypes (dbGaP):

• This public repository obtains and disseminates de-identified data of individual-level phenotype, exposure, genotype, and sequence data. If the study will disclose information to this database, it is suggested that the consent state this information.

Genetic Information Non-discrimination Act (GINA):

• States that health insurers may not use genetic information to make eligibility, coverage, underwriting, or premium-setting decisions. The two exceptions are: 1) Health insurers may request genetic information in the case that coverage of a particular claim would only be appropriate if there is a known genetic risk, and 2) when working in collaboration with external research entities health insurers may request (but not require) that an individual undergo a genetic test. It is suggested this the consent state this information.
Laboratory Requirements

Genetic Tests performed, at least in part, for clinical purposes must be conducted in a NYS-certified lab or obtain a NYS waiver from the requirement by contacting the NYS Office of Civil Rights.

Compliance with CLIA is needed to release information for the health assessment, diagnosis, prevention, or treatment of any disease or impairment of human beings. Laboratories are exempt from CLIA requirements if they are “research laboratories that test human specimens but do not report patient specific results.”

• Laboratories that perform “waived” tests: Laboratories that only perform simple laboratory examinations and procedures that pose no reasonable risk of harm if performed incorrectly may qualify for a certificate of waiver.

• Laboratories that perform moderate and high complexity tests: These laboratories must be issued a Certificate of Compliance by CMS or a Certificate of Accreditation by an approved accreditation organization.

• Laboratories that perform specific specialty and subspecialty testing areas: CLIA has additional requirements for specific testing areas.
Research Focused Approach - Disclose Nothing:

Pros:
• The goal of research is to contribute to generalizable knowledge and not to provide clinical information for an individual. This approach diminishes the idea of a therapeutic misconception.
• It allows for research to be conducted easier and quicker since it removes many obligations concerning appropriate disclosure.

Cons:
• By withholding information from participants, many believe it violates the principle of beneficence which states that researchers should have the welfare of the research participant as a goal of any study.
• By withholding information from participants, many believe it violates their autonomy.
Ethical versus Regulatory

Autonomy Focused Approach - Disclose Everything:
(except when the participant elects not to know)

Pros:
• Being open to participants improves trust with research.
• Improves respects for person by allowing them access to all information learned about themselves.

Cons:
• Significantly increases costs for conducting research due to consent and laboratory requirements.
• Doesn’t treat genetic testing for what it is...Research. As with any other investigation, the results are not guaranteed and should not be treated as such. Disseminating research information as fact increases risk of harm to subjects. Genetic testing results can be wrong in the same manner that a research drug can be harmful.
Balanced Approach - Disclose Some Things:
(Clinically significant information except when the participant elects not to know)

Pros:
• Allows for objective review of results for determining whether they can be appropriately disclosed while taking the participant’s wishes into consideration.

Cons:
• Increases the investigator’s burden to conduct research since each genetic test for each participant would need to be re-assessed for meeting disclosure requirement.
• Increases potential for legal liability
Incidental Findings

When researchers investigate an individual’s DNA sequence for one purpose, they may discover something important that was not part of their original aim. These findings might have clinical significance to the person who gave the sample.

Currently, the only law regarding the return of genetic results and incidental findings is CLIA. As a result of a lack of federal laws, there are many recommendations for how this should be handled by researchers, institutions, and IRBs.

One such suggestion is to design your study to allow for the release of genetic information and incidental findings from the beginning. In addition to complying with the CLIA lab and consent form requirements as detailed by NYS law, the study can categorize incidental findings based on clinical importance along with detailed instructions on handling its possible disclosure.
Incidental Findings

Findings that offer strong net benefits:
• Reveal conditions that are potentially grave or life-threatening, but can be treated (i.e., study reveals phenylketonuria). These findings should be disclosed.

Findings that offer possible net benefits:
• Reveal conditions that would be considered important to the subject, not treatable, but may allow for major life-style changes such as those to minimize susceptibility (i.e., A woman discovered to have BRCA gene mutation will most likely get breast or ovarian cancer. Although there is no cure, the woman may elect to undergo annual cancer screenings, have eggs harvested/frozen for the future, or elect to not have children at all). These findings may be disclosed based on case-by-case assessment.

Findings that have unlikely net benefit:
• Reveal conditions that have no clinical significance and would not lead to a life-threatening condition or have reproductive significance (i.e., misattributed paternity). These findings will not be disclosed.
Incidental Findings

Since each study is unique and the potential incidental findings will vary, the categorization of findings should be worked on with the IRB. While designing the study:

- The protocol should specifically detail the types of findings that would comprise each of the categories.
- The consent should explain incidental findings, detail what types of incidental findings might be found based on the study design, whether they will be disclosed, and whether participants can opt-in or opt-out of receiving information about any or all of the findings no matter the significance or clinical importance.

If based on the protocol, the investigator notes a finding that should be disclosed, the investigator should contact the IRB. In addition to providing information about the incidental finding, the investigator should provide a justification for its disclosure. If the IRB concurs, the results can be disclosed in a manner deemed appropriate by the IRB and researcher.
Case Study

A 21 year old pregnant woman enrolls in a research study being conducted by her prenatal care physician. The study involves determining the genetic likelihood of developing diabetes.

Upon conducting the test’s analysis, the investigator determines that the unborn child has the gene for Huntington Disease. Huntington Disease is a condition that leads to movement impairment and loss of cognitively as an adult. Since it is a dominant trait, the child will get this condition. In addition, that means one of the two parents will also have this condition.

As the investigator and prenatal care physician, what do you do?
Questions to Think About:

1) Is it right to share this information with the woman since the discovery of Huntington Disease is considered an incidental finding?

2) Is it right to share this information taking into account that there are no cures for the condition and it normally doesn’t present until late in age?

3) Is it right to share this information about the fetus since s/he didn’t consent to finding out this information and possibly wouldn’t want to know this information?

4) Is it right to share this information considering that the woman may elect to terminate the pregnancy as a result?

5) Is it right to share the information considering that it means that one of the parents will get Huntington Disease? What if it is the father, who never provided consent for any part of the research study?
QUESTIONS???