Conversations in Ethics

Ethics and Genetics

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Disclosures

Arelis E. Mártir-Negrón, M.D., indicated that neither she nor her spouse/partner has relevant financial relationships with commercial interest companies, and she will not include off-label or unapproved product usage in her presentation or discussion.

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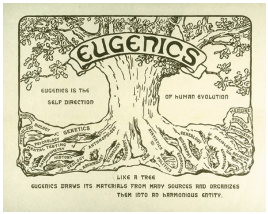
Objectives

- Recognize ethical, legal, and social issues relevant to genetics, genetic counseling and testing.
- Examine the evolution of ethics in genetics throughout history.
- Address unforeseen ethical dilemmas related to advances in medical genetics.
- Apply learned bioethical principles in challenging genetics cases.

Outline

1. Genetics and History
2. Ethics in the Genetics Clinic
3. Preconception, Prenatal and Preimplantation Genetic Diagnosis
4. Genetic Research
5. Gene Editing
6. Genetics and the Law

Genetics and History



Genetics and History: Eugenics

- Eugenics - “well born”
- Theory that humanity could be improved by encouraging the fittest members of society to have more children.
- Positive eugenics: encouraging some to breed
- Negative eugenics: discouraging others

Genetics and History: Eugenics in the United States

- Eugenists advocated for governmental interventions including laws and policies that would give the state direct influence over procreation.
- Thirty-two states passed laws between 1907 and 1937 prescribing state-mandated eugenical sterilization to prevent the birth of people deemed “defective” or “socially inadequate.”

Genetics and History: Eugenics in the United States

“Eugenics thinking” was linked to:

- Laws prohibiting interracial marriage
- Immigration restriction law of 1924 by means of an ethnic/national quota system.
- The idea that taxes would disappear if problem people—criminals, the disabled, and the poor—were no longer born

Genetics and History: Eugenics and the Nazis

- In the early 1930s, laws involving racial/ethnic restrictions on marriage, immigration restriction, and sterilization of "defectives" provided models for Germany's Hitler regime.
- Because of its association with the genocidal intentions of the Nazis, the term *eugenics* has become an all-purpose slur.
- Nuremberg Code, the Declaration of Helsinki, and the Belmont Report were created as answers to the horror of eugenics.

Human Genome Project

- Completed in 2003 - $3 billion
- Determined 3 billion chemical base pairs that make up DNA.
- Identified approximately 20,000-25,000 genes in human DNA.
- Addressed the ethical, legal, and social issues (ELSI)

Ethical, Legal and Social Implications (ELSI)

- 3%-5% of total budget of Human Genome Project
- To identify and address issues raised by genomic research that would affect individuals, families and society.
- Ethical issues in genomic research: presymptomatic screening, carrier screening, workplace genetic screening, testing by insurance companies, ability to manipulate human genotypes and phenotypes

Ethics in the Genetic Consultation

What Happens in a Genetic Consultation?

- In-person consultation with an individual, couple, or family.
- Depending on the specific reason for consultation, the genetic counselor may:
  - ✓ Review personal and family history.
  - ✓ Identify possible genetic risks and discuss inheritance patterns.
  - ✓ Review appropriate genetic testing options.
  - ✓ Provide genetics-related information and reliable sources.
  - ✓ Provide supportive counseling that may help with topics that arise during the consultation.
  - ✓ Discuss prevention strategies, screening tools, disease management.
- Usually takes 0.5 to 1.5 hours

Principles of Bioethics and Genetic Testing

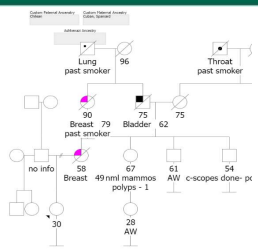
Fundamental bioethics principles apply to issues related to genetic testing:

I. Respect for autonomy
II. Beneficence
III. Nonmaleficence
IV. Justice

I. Respect for Autonomy

- Informed consent
- Privacy and confidentiality
- Protection against coercion
- Refusing treatment

Coercion: Case Example



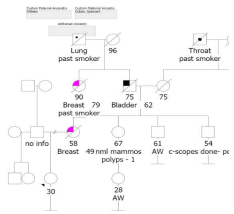
- 30-year-old female with autism
- Her 67-year-old aunt, who is her legal guardian, brought her for genetic testing. Even though she qualifies, she has chosen not to be tested.
- There is concern that her aunt is testing her to justify removal of her ovaries because of concern for unplanned pregnancy.

II. Beneficence: Act to Improve Patient Care

Benefits should outweigh risk:

- ✓Knowledge about risk empowerment
- ✓Information will result in appropriate management
- ✓Accuracy, sensitivity, limitations and genetic test understood

Beneficence: Case Example



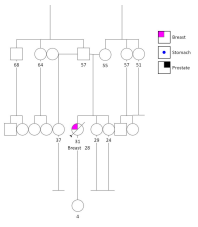
- The proband's genetic testing results could help determine her screening recommendations.
- She could greatly reduce her risk of developing cancer.

III. Nonmaleficence

Address issues related to:

- ✓Psychological well-being
- ✓Family/social relationships
- ✓Children/prenatal diagnosis

Nomaleficence: Non-Paternity Case



- 31-year-old female had genetic testing for treatment purposes but died of stage 4 breast cancer.
- Results were provided to the proband's father, who understood their importance, and scheduled genetic testing for his wife, his other two daughters, and himself.
- Everyone tested negative, and linkage analysis confirmed the initial proband was not his daughter. She was the daughter of his wife.
- The two other daughters were their offspring.

IV. Justice

Govern issues related to society:

- Access to care
  - ✓Risk assessment
  - ✓Genetic testing
  - ✓High-risk management
  - ✓Research protocols
- Standard of care
  - ✓Ensure quality of care provided
  - ✓Protect all stakeholders

Beneficence, Nonmaleficence and Justice Case Examples

- Unaffected 36-year-old woman with strong family history of breast cancer in mother and maternal grandmother. Genetic testing was recommended by her Ob-Gyn in 2015.
- Patient had panel testing, which including *BRCA1*, *BRCA2* and Lynch Syndrome genes.
- Allegedly, she was told by NP that a mutation was identified in *MLH1* and therefore, she had Lynch Syndrome.

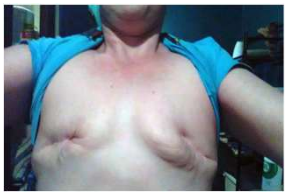
Beneficence, Nonmaleficence and Justice Case Examples

- Mammogram, CA125, and ovarian US were normal
- Allegedly, she was recommended to have a bilateral mastectomy, hysterectomy and bilateral salpingo-oophrectomy*.
- She alleged that after examining her case file with lawyer in 2017 she realized the test result was “negative.”
- She underwent TAH on 8/2016 and bilateral prophylactic mastectomy on 10/2016

*BSO not mentioned in the lawsuit but reported in articles; Daily Mail, October 2017

- Plaintiff reports substantial permanent disfigurement of her breast.
- She is now postmenopausal.

"I'm permanently damaged," she told Time this week. "No amount of money will ever fix what they've done to me. Never." - Plaintiff to Time Magazine, October 25, 2017



Time Magazine

Medical Malpractice/Negligent Diagnosis and Treatment

She is suing the NP, OB-GYN and oncology surgeon for $1.8 million dollars.

(a) In failing to adequately and appropriately review and interpret genetic, pathology, and diagnostic testing results, and in failing to provide to Plaintiff accurate reports and diagnoses in connection with her purported decision to undertake surgical procedures;

(b) In negligently misconstruing Plaintiff's BRAC1 and BRAC2 test results, her Pap-smear results, and in negligently misreporting the results of Plaintiff's mammogram test results, and thereby incorporating them into Plaintiff's care and Assessment and Plan;

(c) In negligently misreporting the results of Plaintiff's genetic testing results, and thereby incorporating the same into Plaintiff's care and Assessment and Plan;

(d) In failing to refer Plaintiff to a genetic counselor before or after undergoing testing as recommended by the National Cancer Institute;

(e) In failing to properly diagnose Plaintiff under the diagnostic criteria for Lynch Syndrome, and in misdiagnosing Lynch Syndrome as a cause for increased risk of breast cancer;

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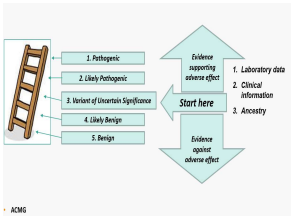
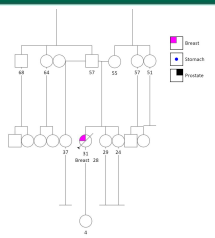
What Was the Mistake?

- Many!! but to name a few:
  - ✓ A variant of uncertain significance (VUS) is NOT a pathogenic result.
  - ✓ Even if it were pathogenic, *MLH1* pathogenic variants are not associated with breast cancer.



Genetic Testing in Children



- The father of the proband's daughter wants the 4-year-old daughter to be tested for the *PALB2* pathogenic variant mutation.

Genetic Testing in Children

- Genetic testing in children is clearly indicated if all these conditions are met:
  - ✓Onset of the disease can occur in childhood
  - ✓Effective intervention is available
  - ✓The genetic test can be adequately interpreted
  - – Examples: neurofibromatosis, MEN1, MEN2, Li Fraumeni, VHL

Genetic Testing in Children

- All bioethical principles could be applied for those in favor of or against genetic testing.
- The ACMG in 2014 recommended that when WES or WGS is performed, the laboratory should report if there is a mutation in 57 specific genes.
- The genes that were selected by ACMG include highly penetrant genes for which treatment and prevention are available.
- When WES or WGS is performed in children (which is usually the case), this contradicts the ACMG previous recommendations.

Genetic Testing for Adult-Onset Disease

- Huntington's disease paradigm for testing for adult onset hereditary disease - The 1994 predictive test guidelines (FN-IHA)
  - These recommendations are revised frequently.
- Genetic Cancer Risk Assessment: a paradigm shift in predicting testing
  - Not 100% penetrant
  - Risk management efficacious
  - Setting standards for predictive testing for common adult diseases

Preconception Genetic Counseling

- Provided for a limited number of severe child-onset diseases
- Provides the individuals with:
  - ✓The chance to pursue assisted reproductive technology (ART) to avoid conception of an affected child
  - ✓Prepare for the birth of a chronically ill child
  - ✓Option for adoption

Prenatal Diagnosis, Prenatal Screening and Disability

- Identifies the presence of one or more specific conditions in the fetus.
  - The degree of accuracy depends on the sensitivity and specificity of the test.
- Screening tests: Quad screening, cell-free DNA
- In order to be diagnostic, a fetal sample is required.
  - CVS or amniocentesis to obtain DNA for karyotype or microarray.
- Termination is not the only reason for prenatal diagnosis. Knowing a child will be born with a medical condition helps prepare parents and medical team.

Prenatal Diagnosis, Prenatal Screening and Disability: Ethical Issues

- Termination of a pregnancy for a nonlethal condition such as Down Syndrome
- Decision to terminate based on screening without diagnostic testing
- Maternal versus fetal rights: respecting maternal autonomy versus acting beneficently toward the fetus

Preimplantation Genetic Diagnosis (PGD)

- PGD, in comparison to prenatal diagnosis, establishes a pregnancy without a mutation, circumventing the potentially difficult decision of termination of pregnancy.
- PGD is expensive because IVF is also needed.
- PGD has ethical considerations because it involves the creation and possible discarding of embryos that have the potential to become viable fetus if transferred to the uterus

Preimplantation Genetic Diagnosis (PGD): Ethical considerations

- Adult-onset disorders
  - ex. Late-onset disorders with low penetrance
- PGD for nonmedical traits
  - ex. gender selection
- Creating a donor sibling
  - ex. HLA match for sibling needing stem cell transplant
- Selecting for disability
  - ex. deaf parents want to select embryo with the mutation associated with deafness

Genetic Research

Gene Therapy: Jesse Gelsinger's Case

- Jesse Gelsinger died at age 29 while undergoing gene therapy.
- He had OTC, a hereditary disease that prevents the body from breaking down ammonia. This condition is lethal without treatment.
- Researchers at the University of Pennsylvania injected working copies of the gene attached to weakened adenovirus. The virus would then infect the liver and integrate the added gene into chromosomal DNA.
- Jesse volunteered for the study, even though it was designed to test possible treatment for newborns. He would not benefit from this study.
- He had an intense inflammatory reaction, ARDS, DIC, and multiple organ failure.

www.jesse-gelsinger.com

Gene Therapy: Jesse Gelsinger's Case Ethical Issues

Selection of subjects: Jesse had a mild case of OTC; the investigators were concerned with the difficulty of obtaining informed consent from parents of newborns with the lethal form of OTC. Adults, even though less affected, would be easier to consent from.

Informed consent: The investigators failed to inform Jesse and other volunteers about the adverse effects observed during animal studies, with some animals getting sick and even dying with the vector (virus).

Conflict of interest: Dr. Wilson, the lead scientist, had financial interest in the development of the adenovirus vector that was used in the OTC gene therapy trial.

The Havasupai Indian Case

- In 1990, researchers from Arizona State University (ASU) began collecting DNA samples from the Havasupai Indians to research diabetes.
- The tribe later learned that their blood samples were being used for other studies, including mental illness and alcoholism, and to determine the tribe's geographical origins, "without their consent."
- ASU was sued by the tribe. In 2010 a monetary settlement was reached and the blood samples were returned.
- A moratorium on genetics research was enacted by various Native American tribes.

Genetic Research: The Havasupai Indian Case

Informed consent:

- Obtaining consent for community-based participatory research (CBPR) is difficult, time-consuming, and challenging.
- Open communication is important, as well as knowledge of the population. The full extent of research and goals must be communicated.
- Education and language barriers must be considered during the process to obtain informed consent, especially in a vulnerable population.

Genetic Research: The Havasupai Indian Case

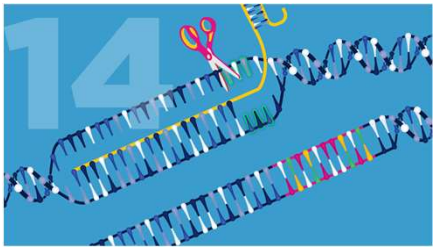
Justice

- According to the late Hopi geneticist Dr. Frank Dukepoo regarding DNA and biological materials in Native Americans:

"To us, any part of ourselves is sacred. Scientists say it's just DNA. For an Indian it is not just DNA; it's part of a person, it's sacred with deep religious significance. It is part of the essence of a person." (Petit 1998).

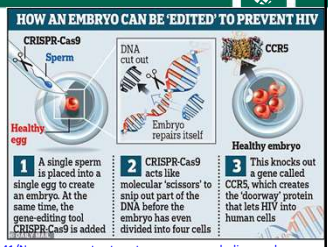
- No formal legal precedent came from this case because it was settled out of court.

Gene Editing



Gene Editing: The Case in Human Embryos

- November 2018: during the 2nd International Summit of Human Genetics, He Jiankui, a Chinese researcher, claimed that he edited two human embryos to prevent HIV.
- He achieved this with CRISPR gene editing



https://www.dailymail.co.uk/sciencetech/article-7752141/Never-seen-extracts-outrageous-research-disgraced-scientist-Jiankui.html

Gene Editing

- Jiankui claimed it was germline gene therapy, which is different from somatic therapies.
  - Somatic gene therapies involve modifying a patient's DNA to treat or cure a disease caused by a genetic mutation.
  - Germline editing affects all cells in the organism, including eggs and sperm, so its effects are passed through generations.
- The consequences are difficult to predict.
- A moratorium for germline editing was called by the scientific community

Gene Editing

- This technology offers hope to editing cruel mutations out of the gene pool; however, the cost is prohibitive for some.
- Where do we draw the line between disease treatment and enhancement? Was it necessary to edit to prevent HIV in the fetuses?
- How will the scientific community create regulations for a technology that is relative to use?

Gene Editing

- There is a need for defined guidelines.
- Experts from different countries must come together to form a consensus of what clinical applications are acceptable.
- Overregulation may delay science.
- "Public policy or ethical discussion that's divorced from how science is progressing is problematic."

- Glenn Cohen, faculty director of the Petrie-Flom for Health Law Policy, Biotechnology and Bioethics, Harvard Law School

Genetics and the Law

The Law of Genetic Privacy

- The right to privacy refers to the ethical and legal principles that recognize the importance of limited access to an individual or information about an individual.
- Genetic information has implications for current and future health of individuals and their family, with major social and economic consequences

doi:10.1093/1093/jlb/lsz007

The Law of Genetic Privacy

- Confidentiality: nondisclosure of genetic information
- Should genetics be considered like any other health information?
  - ✓Contains tremendous amount of information
  - ✓Immutability
  - ✓Potential use as a unique identifier
  - ✓Implications for family members
  - ✓Implications for others with similar geographic ancestry

The Law of Genetic Privacy: Genetic Information (GI) in Healthcare

- Breaches in privacy, confidentiality, and security may occur:
  - ✓GI disclosed or access granted to health providers without authority or legitimate need for this information.
  - ✓GI obtained and disclosed is beyond what is needed for legitimate healthcare purposes.
  - ✓GI is used for a purpose unrelated to the disclosure.
- The term “genetic exceptionalism” has been proposed.

The Law of Genetic Privacy: Health Insurance Portability and Accountability Act (HIPAA, 2006)

Does:

- State that genetic information cannot be used to deny or limit coverage for members of group plans
- Prevent insurers from charging different individual premiums within a group plan.
- Give the US Department of Heath and Human Services (HHS) jurisdiction to regulate entities that provide healthcare or pay for it (insurers)

The Law of Genetic Privacy: Health Insurance Portability and Accountability Act (HIPAA)

Does not:

- Give HHS the jurisdiction to regulate other private companies and institutions:
  - Drug manufacturers
  - Research institutions that provide no health services
  - Companies that use fitness tracking devices
  - Direct-to-consumer (DTC) genetic testing services

  Which, in current times, use and store health and genetic data

Genetic Information Non-Discrimination Act (GINA, 2008)

- Prohibits employers from requesting, requiring, or purchasing genetic information with respect to an employee (including an applicant) or family member of the employee.
- Provides that genetic information “shall be treated as health information” (no genetic exceptionalism) as in HIPAA
- Privacy rule applies only to healthcare payment chain, does not to life, long-term care, DTC, and others.

Genetic Information Nondiscrimination Act (GINA, 2008) and Affordable Care Act (ACA, 2010)

- GINA
  - ✓Protects asymptomatic individuals against discrimination based on their genetic information in health coverage and in employment
  - ✓Does not protect against discrimination for life, disability, and long-term care coverage.
- ACA
  - ✓Prohibits all health-based discrimination in health insurance

Informing At-Risk Relatives

- Clinicians should advise their patients about the importance of discussing with their relatives a significant diagnosis or predictive genetic information.
- Duty to contact relative: judicial opinion predates HIPAA, which prohibits nonconsensual disclosure.
- "As a matter of ethics and law, clinicians are neither required nor permitted to inform the genetically at-risk relative of their patients without the consent or authorization of their patient or their patient's personal representative."

doi:10.1093/1093/jlb/lsz007

Genetic Information in Direct-to-Consumer Genetic Testing

- Companies now provide genetic insights into:
  - ✓Health
  - ✓Ancestry/genealogy
  - ✓Family relationships
  - ✓Lifestyle choices
- These companies do their own genetic testing, but some ask consumers to upload information

Genetic Information in Direct-to-Consumer Genetic Testing

- Findings of these tests may be disruptive
  - ✓Identify birth parents in adopted individuals
  - ✓Identify gamete donors, which may lead to unwanted contact.
- These efforts to define biological relationships require sharing genetic data.

Genetic Information in Direct-to-Consumer Genetic Testing

- Companies are beginning to provide health-related genetic tests without involvement of a healthcare provider.
- 23andMe obtained authorization from FDA to market Genetic Health Risk (GHR) for 10 conditions in 2017, and for *BRCA1/2* AJ variants in 2018.
- Authorization was also granted for a pharmacogenetics test.

Genetic Information in Direct-to-Consumer Genetic Testing (DTC-GT)

In 2017, a study of 90 DTC-GT investigated the data that companies provide to consumers about their genetic data practice.

35 out of 90 provided no information about their genetic practices, including samples and genetic data.

Of the 55 providing information:

- ✓only half disclosed whether or not data would be stored; some would retain sample.
- ✓23 had policies with provisions that indicated data would or might be shared with third parties, but with no list provided.

Genetic Information in Direct-to-Consumer Genetic Testing (DTC-GT)

- 18 companies would share deidentified data with third parties without further consent.
- 10 companies allowed participants to opt in for sharing data with outside researchers.
- 38 companies would share data with government and law enforcement only “as required by law.”

Genetic Information in Direct-to-Consumer Genetic Testing (DTC-GT)

- These companies typically are not subjected to laws that apply in the clinical setting, such as HIPAA and CLIA.
- “State laws may provide consumers with potential cause for action against DTC in certain circumstances; the efforts are complicated by the fact that consumers agree to terms and conditions that limit these companies” liabilities or provisions that limits the remedies and damages available to the consumer.”

doi:10.1093/1093/jlb/lsz007

Privacy Best Practice for Consumer Genetic Testing Practices (2018)

- Released in 2018 in Future of Privacy Forum, this document was produced with leading DTC-GT companies and consumer and privacy advocates.
- Addresses collection, retention, use, sharing and research basis of genetic testing.
- Voluntary and lack of enforcement mechanism.
- Does not place restriction on unidentified data.

Summary

- The field of genetics holds great potential. We can learn from history to avoid repeating mistakes.
- Mechanisms should always be in place to protect the individual; ethics principles are key for protection.
- Genetic evaluations, which include professionals trained not only in science but also in psychosocial studies, are always important to guide the patient to the best decision.
- Genetic counseling is non-directive but presents the patient with different options to help with the decision-making process.

Summary

- Prenatal and pre-implantation genetics are two of the most difficult areas of genetics because of the concern for eugenics. However, these areas offer hope to parents with the potential to have a child with a fatal condition. Regulation is needed in the United States.
- Advances in genetics and technology are helping to improve medicine by finding causes of disease, effective medicines and life-saving genetic testing, and by creating future possibilities with gene therapy and genetic engineering.
- Global scientific/medical entities need to collaborate for the benefit of the individuals, balancing regulation without delaying advances in science.

Summary

- Genetic literacy is important when training healthcare providers, especially physicians, to avoid error in interpretation which could cause harm to patient. When in doubt, ask!

Summary

- "Few, if any, applicable legal doctrines or enactments provide adequate protection or meaningful control to individuals over disclosures that may affect them."
  Clayton et al, Journal of Law and Bioscience, 2019
- Therefore, laws protecting genetic data are important. Congress must act.

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Thanks!