Ethical, Legal, and Social Issues (ELSI) of Genomics Research
Corinne Engelman, MSPH, PhD; Robert Banks, MA

Overview
This genetics lesson was designed to first provide high school biology students with a general understanding of the non-Mendelian inheritance patterns of complex diseases and traits and then to show how this understanding is important in thinking about the ethical, legal, and social issues (ELSI) of applications of genomics research (for example, direct-to-consumer genetic testing). Since many of these high school students will not attend college or gain further training in genetics, we sought to provide the tools for them to become educated citizens with respect to genomic issues they may be exposed to by the media.

In previous units, students encountered basic genetic ideas such as dominant vs. recessive and Punnett Squares, but our aim for this unit was to give students an appreciation for the complications of genetics in common diseases. It was hoped that after completing this unit, students would 1) be aware of the multiple factors that contribute to common diseases, 2) be aware of how genomic research and knowledge affects their lives and the world around them, and 3) be able to use their scientific knowledge to think critically about the implications of genomic research to each student’s individual life, the lives of other individuals, and society as a whole.

Student Population
This lesson was designed for the Introduction to Genetics class at Malcolm Shabazz City High School in Madison, WI. Shabazz is an alternative school serving a predominately at-risk student population. Thirty percent of the students receive free or reduced lunch. Although there is no formally collected data, there is an estimated 20-30% LGBT (lesbian, gay, bisexual, transgender) student population. Individual classes serve combined 9-12th grade levels and are intended to operate on nine-week quarters with as few prerequisites as possible, making continuity from quarter to quarter quite difficult. Most of the students are quite bright but severely lacking in academic skills due to the inability to “fit in” at the regular community high schools. Many are resistant to engaging in a standard approach to the learning process. However, nearly 80% of Shabazz graduates will participate in post-secondary education, either two year or four year college programs, within five years of graduating from high school.

Scope and Sequence
The academic year is divided into four nine-week quarters, and the Introduction to Genetics course has the prerequisite of at least one introductory biology course. The collaborative unit was a 17-day series of activities that took place in March 2009 and concluded the third quarter of the academic school year. Before this unit began, students were introduced to the concepts of the chromosomal basis of inheritance, Mendelian inheritance patterns, molecular basis of
inheritance, structure and form of chromosomes, DNA, meiosis, and various types of chromosomal and point mutation disorders. This unit was designed to expose students to the complexities of genetics and to relate these complexities to the lives of the students through ELSI. Another purpose was to encourage students to become more scientifically literate citizens who would be aware of and able to develop informed opinions about legislation such as the Genetic Information Nondiscrimination Act (GINA), and have the knowledge and skills to critically evaluate the claims of commercially available genetic testing and reports in the mass media about issues related to genetics.

**Wisconsin State Standards Addressed, Grade 12:**
- Standard A – Science Connections: A.12.2 Show how conflicting assumptions about science themes lead to different opinions and decisions about evolution, health, population, longevity, education, and use of resources, and show how these opinions and decisions have diverse effects on an individual, a community, and a country, both now and in the future.
- Standard F – Life and Environmental Science: F.12.3 Explain current scientific ideas and information about the molecular and genetic basis of heredity.
- Standard F – Life and Environmental Science: F.12.4 State the relationships between functions of the cell and functions of the organism as related to genetics and heredity.
- Standard G – Science Applications: G.12.3 Analyze the costs, benefits, or problems resulting from a scientific or technological innovation, including implications for the individual and the community.
- Standard G – Science Applications: G.12.4 Show how a major scientific or technological change has had an impact on work, leisure, or the home.
- Standard G – Science Applications: G.12.5 Choose a specific problem in our society, identify alternative scientific or technological solutions to that problem and argue its merits.
- Standard H – Science in Personal and Social Perspectives: H.12.5 Investigate how current plans or proposals concerning resource management, scientific knowledge, or technological development will have an impact on the environment, ecology, and quality of life in a community or region.

**Science Concepts Addressed**
- Exceptions to Mendelian inheritance patterns including, mosaicism and mitochondrial inheritance
- Penetrance
- Variable expressivity
- Epigenetic modifications and paternal imprinting
- Phenocopies
- Genetic heterogeneity
- Phenotypic heterogeneity
- Pleiotropy
- Gene-gene and gene-environment interactions

Likely Student Misconceptions
- Genes alone determine physical and behavioral phenotypes.
- Our understanding of genetics and technology related to genetics is more advanced than it really is.
- All or most risk alleles are fully penetrant.
- Only people with rare genetic conditions are affected by policies and programs designed to regulate/restrict healthcare, insurance, and job protections.

Learning Outcomes
- Most diseases and traits do not strictly adhere to Mendel’s laws of inheritance.
- Environment plays an important role in most diseases and traits.
- Most common diseases and traits are not well understood and risk cannot yet be predicted with accuracy.
- Genomic research affects society as a whole and every individual in society.
- There are many ELSI related to genomic research, which are complicated and require both scientific knowledge and critical thinking to solve.
- Provide the tools to critically evaluate information presented by the media regarding genomics.

Module Outline
1. Pre-Unit Assessment: 1 class
   - Purpose: to assess the students’ prior knowledge and understanding of genetic materials and what they think is on the forefront of genetic research today
   - Activities
     - *Genetics pretest:* traditional quiz to evaluate what students know about the basics of molecular biology, inheritance, and ELSI
     - *Current events article:* students imagine that they are a journalist for the popular press and write an article about a breaking genetic research discovery

2. Non-Mendelian Inheritance: 3 classes
   - Purpose: to teach students about the complexities of genetic diseases and the role environment plays in influencing risk for disease
   - Activities
     - *Lecture:* PowerPoint presentation by Dr. Engelman
     - *Patient FAQ:* students select a genetic disease of their choice and research it, using suggested online resources to compile a mock Frequently Asked Questions sheet that would be given to patients with that diagnosis
3. Commercial Testing for Complex Diseases: 2 classes
   • Purpose: to get students thinking about the reliability and ramifications of direct-to-consumer genetic tests
   • Activities
     o *Spit Party:* students research and discuss “spit parties,” receive a set of mock results from submitting a DNA sample to a commercial testing company, and fill out a worksheet assessing their trust in the results and how their behaviors and lifestyles may change based on their test results

4. Guided Reading: 3 classes
   • Purpose: to introduce students to ELSI concepts from reading passages
   • Activities
     o *Guided Reading:* students independently read assigned passages from McCabe & McCabe (see Source Materials), following the instructor’s model of reading for understanding in the sciences, and complete a guided reading worksheet

5. Individual Reading and Poster Session: 3 classes
   • Purpose: to expose students to several ELSI topics from McCabe & McCabe in a short time and provide them with an opportunity to share the knowledge they gained from independent readings
   • Activities
     o *Poster Session:* each student creates a poster or PowerPoint presentation to explain the main points of their assigned chapter to share with the rest of the class

6. ELSI Scenarios and Role Play: 5 classes
   • Purpose: to make students aware of the possible consequences of genetic information and how the scientific and legal communities have worked to deal with them
   • Activities
     o *ELSI Scenarios:* students are divided into small groups and assigned an ELSI scenario, then researched background information to prepare arguments for both positions surrounding the scenario
     o *Debate:* students are assigned a side/perspective and debate with their opponents who have researched the same scenario

**Post-Intervention Insights**
1. Pre-Unit Assessment
   • In general, most students seemed to make an effort to write a realistic story. However, some wrote outrageous or futuristic stories, and most students included at least one statement of this nature. Next year we will
(please do make an attempt to write a realistic article, not one that is futuristic or outrageous).

2. Non-Mendelian Inheritance
   - Students were able to grasp the mechanical aspects of complex inheritance and could research and report back accurately on mechanisms, effects, and inheritance of disorders.

3. Commercial Testing for Complex Diseases
   - Students were not able to use what they learned about non-Mendelian inheritance to think critically about their direct-to-consumer test results. For example, one student who got results back saying she was at decreased risk for skin cancer said she would stop using sun block, and when she was given results indicating she was at high risk for lactose intolerance said she would stop consuming milk products even if she didn't have any symptoms yet. Next year, we plan to combine this exercise with the FAQ from the non-Mendelian inheritance lesson so each student will thoroughly research the diseases they are at high or low risk for and create an FAQ for those diseases. They will then answer the questions about how reliable they think the results are and how the results will affect their behavior in the future.

4. Guided Reading
   - Students were able to understand and critique genetic determinism as evidenced during classroom discussion.

5. Individual Reading and Poster Session
   - This went relatively well with the exception of the poster presentation format. Next year we will restructure this so that each student will get to give a short poster presentation standing by their poster as well as view all the other students’ posters.

6. ELSI Scenarios and Role Play
   - The poster session was inadequate preparation for the ELSI debate that followed. We believe that this was due to the students being unable to read and discuss how all the aspects discussed were interconnected.
   - More time was needed to read and discuss McCabe & McCabe. The authors provide a comprehensive exploration of both the scientific and ELSI related to genetics.
   - Students struggled more than anticipated with ELSI. The most glaring issue was the inability to clearly differentiate between ethical and legal issues. Many students seemed to take the view that if something was legal than it was also ethical, at least as far as genetics are concerned, although many of these students do not take the same view on issues of racial, sex, or gender discrimination.
   - Students needed a lot of guidance on how insurance policies work and how these could relate to genetic discrimination.

7. General
   - Mr. Banks plans to expand this unit to a full quarter-long class by covering more of the McCabe & McCabe book as a group. Dr. Engelman would participate with contributions similar to those of this year spread out over
Mr. Banks would also plan a new one-quarter course to cover the molecular, chromosomal, and Mendelian inheritance aspects that perceived to be essential prerequisites for ELSI-related topics. Additional lessons would utilize actual journal publications about ELSI so that students have more exposure the thinking process behind legal and ethical discussions in the field.

**Source Materials**


ELSI Scenarios 1 and 8 are courtesy of Alexandria Yonker, MS, CGC.

**Unit Materials**
All unit materials are provided, in the order in which they were introduced to the students, on the following pages.
Genetics Pretest

A. You are about to learn about non-Mendelian patterns of inheritance. Based on what you already know describe what you might expect to see in a non-Mendelian pattern.

The following questions are intended to allow me to understand your current understanding of the science of genetics and how you think this area of science affects other aspects of your life and the lives of others. Please provide thoughtful answers. There are no “right” or “wrong” answers, and achieving credit for this assignment only depends on answering completely and seriously all of the questions.

For the following questions indicate with a number (see below) how strongly you agree with or disagree with the statement.

1=strongly agree  2=agree  3=no opinion  4=disagree  5=strongly disagree

1. Genes have strict control over the expression of most genetic traits.

   ______

2. Current genetic testing procedures for common diseases, like breast cancer and Alzheimer’s, accurately predict the occurrence of disease.

   ______

3. Employers can hire or fire someone based on the results of a genetic test.

   ______

4. Sexual preference is known to be a trait controlled by genes.

   ______

5. Gender, in humans, is controlled by whether or not you have an XX or XY set of chromosomes.

   ______
For each of the following questions make sure to provide a brief but complete explanation for your reasoning.

6. What agency, either governmental or private, should have access to the genetic histories of people?

7. Does your answer change if this information could allow for increased quality of health services?

8. Does your answer change if your taxes or other expenses could be reduced if this knowledge was shared?

9. Are there situations where the good of the society outweighs the individual privacy rights?
Genetics in the News

You are a journalist working for a mainstream newspaper (The New York Times) or magazine (TIME). Without looking up any real current events, write a short article for your publication discussing “breaking news” in the field of genetics geared toward your audience: the general public reading the popular press. Your article will not be graded for factual content – we want to see what you think is making the headlines in genetics news and experiments (please do make an attempt to write a realistic article, not one that is futuristic or outrageous).

Your article should be one half to one full page, single spaced. Please use 12-point Times New Roman or Arial type and 1 inch margins.
Complex Inheritance

Corinne Engelman
March 2009

Exceptions to Traditional Mendelian Inheritance Patterns

Genotype ≠ Phenotype

(pair of alleles at a locus)

(observable physical, biochemical, psychological trait that may be influenced by genotype)
Mosaicism

- Mutation that occurs after the formation of the zygote
- Developing organism contains some cells with mutation and some without
- Can result in mild form of phenotype in the individual, but more severe form in offspring
- If mutation occurs in a cell destined for the germline, the individual will be an unaffected carrier, but offspring will have full phenotypic expression (if dominant disease/trait)
- Still Mendelian inheritance, but won’t look like it is phenotypically
Mitochondrial Inheritance

- A zygote receives most of its mitochondria from the egg, not the sperm.

- Expression of mitochondrial gene mutations typically follows a pattern of maternal inheritance:
  - All offspring (both sexes) of an affected woman receive copies of the mutant gene.
  - No offspring of an affected man receive copies of the mutant gene.
  - Currently ~2 dozen phenotypes related to mitochondrial DNA mutations.

http://www.neurocast.com/site/content/sessions_02_2002.asp
Complete Penetrance

- genotype=disease

- **Causative genes**
  - *APP*, *PS1*, and *PS2* genes for early-onset AD

Incomplete Penetrance

- A fraction of the individuals who inherit a disease allele will not develop the disease, or the appearance of the condition may depend on other factors such as age, gender, or environment

- **Susceptibility genes**
  - *BRCA1* and *BRCA2* genes for breast cancer
  - *APOE* gene for late-onset AD
Variable Expressivity

- Variations in the degree of manifestation of a disease/trait
  - Neurofibromatosis: phenotype varies from café-au-lait spots on the skin to a systemic involvement and tumors of the skin

- **Anticipation**: a special case of variable expressivity where the severity of the expression becomes greater and/or manifests earlier in successive generations
  - Myotonic dystrophy: severity of phenotype increases with each generation due to an amplification (increase) in a trinucleotide repeat

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Variable Expressivity

- **Intrafamilial** variability of expression may be due to factors such as GxG and GxE interactions, chance, and mosaicism

- **Interfamilial** variability of expression may be due to the factors above plus genetic heterogeneity

  - Phenotype is caused by any one of multiple genotypes
In all conditions of postnatal onset, penetrance depends on the age of the individual: the older the age, the higher the probability for affection/disease.

Can use information on **age-at-onset** in many ways:
- Genetic counseling
- Differentiation of etiologies
- Genetic studies (inclusion criteria, stratification, or as outcome)

Makes it hard to study the disease: misclassification of disease status due to variable age-at-onset.
Age-at-Onset as an Outcome

- Mean age at onset:
  - No risk alleles: 84.3
  - 1 risk allele: 75.5
  - 2 risk alleles: 68.4
- % diagnosed with AD at age 75:
  - No risk alleles: 24%
  - 1 risk allele: 61%
  - 2 risk alleles: 86%

Corder et al., Science 1993 Aug 13; 261(5123):921-3

Epigenetic Modifications

- **Imprinting** or the parent of origin effect: suppression of expression depending on gender of parent from whom the allele is inherited

- Cause: Imprinting is established during the development of sperms or eggs by **methylation**, a chemical modification in the bases of DNA, which is correlated with the functional activity of DNA (**epigenome**)

- Example: **Paternal imprinting (suppression) = maternal expression**
  - Paternally transmitted allele is not expressed; only expressed when transmitted from the mother
Paternal Imprinting

The phenotype is expressed only when the mutant allele is inherited from the mother. Thus, mutant imprinted alleles can remain masked when they are paternally inherited, but clinically re-appear in one-half of children of carrier daughters.


Phenocopy

An environmentally caused phenotype that mimics a genetic trait or syndrome

Example: Type 2 diabetes
### Genetic Heterogeneity

- When a phenotype is caused by any one of multiple genotypes
- Same phenotype, different genotypes
- 2 types:
  - **Allelic heterogeneity**: phenotype caused by more than one allele in a given gene
  - **Locus heterogeneity**: phenotype caused by more than one susceptibility gene

### Allelic Heterogeneity: CF

- More than 1000 unique mutations in the *CFTR* gene have been identified
- One mutation accounts for ~70% of cases in U.S.
- Relationship between severity of disease and specific mutation
Phenotypic Heterogeneity

- The same disease shows different features in different families or subgroups of patients
  - Different ages of onset
  - Different clinical features
  - Variable expressivity
- The differences could be due to genetic heterogeneity, GxG, or GxE interactions
- Example: CF
Pleiotropy

- More than one phenotype is caused by allelic mutations at a single locus
- Example: APOE is involved in removing fats from the blood stream and is associated with:
  - Elevated serum cholesterol and triglycerides → atherosclerosis, premature coronary artery and peripheral vascular disease
  - Late-onset AD
  - “Diseasome”

Gene-Gene Interactions

Mark Daly and David Altshuler Nature Genetics 2005, Volume 37, Number 4
Gene-Environment Interactions

- "Genetics loads the gun and environment pulls the trigger" – Judith Stern

- Environmental (nongenetic) factors interact with genetic predisposition (susceptibility genotypes)

- Environmental factors can be from embryonic development through adulthood

- Example: PKU
  - Genotype + exposure to the amino acid phenylalanine in dietary protein = mental retardation (need both to get phenotype)

- Public health implications
Questions?
- What is the name of my disease? Are there any other common “nicknames” I may have heard before? What is my disease?

- How did I get this disease?

- What could I have done to prevent the onset of this disease?

- How old are other patients with this disease?

- What are the symptoms associated with this disease? How long will they last?

- What can I do to control my symptoms?

- Is there a cure for this disease?

- What sources can I turn to for more information?
Nonmendelian Genetic Disease List (noncomprehensive)

Celiac Disease
Alzheimer Disease
Multiple Sclerosis
Breast Cancer
Ovarian Cancer
Colorectal Cancer
Prader-Willi Syndrome
Angelman Syndrome
Huntington Disease
Fragile X
Inherited Deafness (Waardenburg Syndrome)
Phenylketonuria
Li-Fraumeni Syndrome
Heart Disease
Type 1 Diabetes
Type 2 Diabetes
Schizophrenia
22q11 Syndrome
Neurofibromatosis
Sickle Cell Disease
Autism
Crohn’s Disease
Muscular Dystrophy
Disease FAQ Sources

**www.google.com** Google: general search engine. Look for national organizations, associations, support groups for the disease

**www.wikipedia.org** Wikipedia: free online user-contributed encyclopedia. Also check the “sources” section at the bottom of the article for further references.

**health.nih.gov** National Institutes of Health: the nation’s medical research agency. Browse general health topics alphabetically.


**www.geneticalliance.org** Genetic Alliance: not-for-profit organization providing information to genetic consumers, researchers, and industry. Listings of genetic diseases as well as corresponding organizations.

**www.kumc.edu/gec/support/** University of Kansas Medical Center. Listing of rare and genetic conditions and information.

**www.webmd.com** WebMD. Consumer health site with symptom and treatment information on many common and rare diseases.

**www.medicinenet.com** MedicineNet. Informational database of diseases, symptoms, procedures, and tests.
1. What diseases or health problems are you at a higher risk for?

2. Based on the information on the 23andMe website and other information from the websites you used for the FAQ exercise, how reliable do you think the results are for the diseases or health problems you are at higher risk for?

3. How will these results affect your behavior in the future?

4. What diseases or health problems are you at a lower risk for?

5. Based on the information on the 23andMe website and other information from the websites you used for the FAQ exercise, how reliable do you think the results are for the diseases or health problems you are at lower risk for?

6. How will these results affect your behavior in the future?
Results from the 23andMe “spit party”

**Clinical Reports**

- Celiac Disease: Higher risk than average
- Cystic Fibrosis: Non-carrier
- Lactose Intolerance: Average risk
- Resistance to HIV/AIDS: More resistant
- Type 2 Diabetes: Average risk

**Research Reports**

- Bipolar Disorder: Higher risk than average
- Colorectal Cancer: Average risk
- Heart Attack: Average risk
- High Blood Pressure (hypertension): Average risk
- Lou Gehrig’s Disease (ALS): Average risk
- Lung Cancer: Lower risk than average
- Obesity: Average risk
- Schizophrenia: Average risk
- Skin Cancer: Average risk
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<td>Higher risk than average</td>
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<table>
<thead>
<tr>
<th>Research Reports</th>
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<tr>
<td>Bipolar Disorder</td>
<td>Average risk</td>
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<tr>
<td>Colorectal Cancer</td>
<td>Average risk</td>
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<tr>
<td>Heart Attack</td>
<td>Average risk</td>
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<tr>
<td>High Blood Pressure (hypertension)</td>
<td>Average risk</td>
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<tr>
<td>Lou Gehrig’s Disease (ALS)</td>
<td>Average risk</td>
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<tr>
<td>Lung Cancer</td>
<td>Lower risk than average</td>
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<td>Obesity</td>
<td>Average risk</td>
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<tr>
<td>Schizophrenia</td>
<td>Average risk</td>
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<tr>
<td>Skin Cancer</td>
<td>Higher risk than average</td>
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Results from the 23andMe “spit party”
Reading Guide For Genetics

For all the following questions provide evidence from the reading such as which paragraph, quotes, etc. where it is appropriate to do so. The reading guide is intended to help you to more carefully consider the content, intent, and relevance of the reading. You can use the reading guide to help you during class discussions or on any written assignments you may have during the quarter. The contents of the reading guide will be read only by Robert, Dr. Engelman, and yourself.

1. What is the main topic of this chapter?

2. Briefly describe how your understanding of the topic changed as you read the chapter.

3. What thoughts or questions would you like to have shared or asked the authors about that are relevant to the content of the chapter?
4. To what other chapter that you’ve already read does this chapter most closely relate? Briefly explain.

5. Does anything from this chapter resonate with your own personal experience? If so, briefly explain.
DNA: Promise and Peril Poster Session Guidelines

Your poster should describe the chapter so that someone who did not read the chapter could come away after studying the poster as if he/she had read it. Questions that should be answered on the poster should include at least the following:

What is the main topic of this chapter?

What is the ethical, legal, or social component of this issue?

What is the “state of the art” of our knowledge concerning the science discussed in this chapter?

What is/are the common misconceptions held by the public about this topic/area of research?

How does this research/topic weaken a deterministic view of genetics?

You should also be able to answer any questions that your classmates or Robert may have about the chapter you’ve read. If you cannot answer it is permissible to direct someone to the exact place in the reading or an outside source where he/she could find the answer.
ELSI Scenario 1

You are a prenatal genetic counselor at a city hospital. A woman comes in to your clinic to visit with you and is 7 weeks pregnant. She informs you that her husband has a family history of Huntington Disease (HD). His father was diagnosed with the condition at age 42 and died 2 years ago at the age of 56, and his sister tested positive for HD last year at age 32. His sister is not yet symptomatic, but elected to undergo presymptomatic testing saying “I just couldn’t live with this hanging over my head and not knowing.” Your patient’s husband is 28 years old and, she claims, has stated emphatically that he does not want to be tested. He has a 30-year-old brother who has also elected not to undergo pre-symptomatic testing.

Your patient is very concerned about this family history. She says watching her father-in-law deteriorate for years before finally dying unable to recognize those around him or provide even the most basic care for himself was incredibly painful. She disagrees with her husband’s decision not to be tested; she wants as much information as possible. She says they have had many discussions about the subject, most of which have ended up as arguments. Her husband now says he does not want to talk about this anymore.

Your patient is asking for prenatal testing to determine whether or not her baby has the genetic mutation which causes Huntington Disease. The test is possible, but is not routine. If the test result comes back negative for the mutation, your patient informs you she plans to carry the pregnancy to term and not inform her husband she had the testing done. If the test result comes back positive for the mutation, she intends to tell her husband the result and discuss terminating the pregnancy with him. You remind your patient that a positive result for the baby would also indicate a positive result for her husband, as your patient has no family history of Huntington Disease herself. Your patient responds that this baby is just as much hers as it is his and she cannot continue the pregnancy without knowing what lies ahead. She says she has experienced a lot of stress and is worried that if she does not get any answers soon, she may lose the baby anyway as she typically has somewhat high blood pressure even without high levels of stress.

What would your next steps be? Would you, as a professional, perform this test? What ethical challenges do you identify in this scenario? Are there any legal considerations? What implications does this test have for your patient? For her family? Does this scenario and similar ones have any greater implications for the medical community and for society?
ELSI Scenario 8

A gifted athlete who led his college football team to the national championship has achieved his life's ambition of playing professional football. When he went pro, he signed a long term contract worth $50 million over eight years. Throughout his first three seasons, his performance has not lived up to his coach's high expectations, and there has been talk that the team would like to trade him.

During a recent routine physical, team doctors offer the option for all players to take a series of genetic tests that would determine whether any players had a likelihood of developing heart disease. The doctors tell the players that the tests could inform them of potential increased risks for heart disease, but will not actually tell them if they have the disease. Though the team is not requiring any player to take the tests, they tell players that if a test gives a positive result, they won't be able to play football because football players are put through strenuous amounts of exercise that may put too much stress on their hearts. The team argues that learning such information could be extremely valuable and potentially life-saving to its players.

After hearing all of the information and weighing the potential consequences, this athlete chooses to take the genetic tests. Based on the results of the tests, doctors learn that he has a 25 percent chance of developing a specific heart disease that causes the heart muscle to thicken and work less efficiently. Because his football team does not want to take any chances, the front office decides to release him from his $50 million contract on medical grounds, even though he may not ever develop any sort of heart disease.

Is this athlete’s dismissal from the team legal? Is it ethical? Is there any justification for using a genetic test result showing a predisposition for a medical condition (and not a medical condition itself) to determine terms of employment? What implications does this test result have for the athlete? For his family? For other team members? Does this scenario and similar ones have any greater implications for the medical community and for society?
Using preimplantation genetic diagnosis to save a sibling: the story of Molly and Adam Nash by Bonnie Steinbock

Molly Nash was born on July 4, 1994 with multiple birth defects due to Fanconi anemia, a deadly genetic disease that causes bone marrow failure, eventually resulting in leukemia and other forms of cancer. Her best chance for survival was a bone marrow transplant from a perfectly matched sibling donor. Lisa and Jack Nash had considered having another child, not as a source of bone marrow but because they very much wanted another child. They had decided against it because there was a one-in-four chance that the infant would have the same illness as Molly, and aborting an affected fetus was not an option Mrs. Nash would consider. Then they learned about preimplantation genetic diagnosis (PGD), which would enable them to screen embryos for the disease, and implant only the healthy ones. Moreover, the embryos could also be tested to find which ones shared Molly’s tissue type. The baby would be not only disease-free, but could also provide bone marrow to Molly. Moreover, because blood cells saved from the baby’s umbilical cord and placenta could be used, there would be no need to extract the bone marrow from the baby’s body, a procedure which is both painful and carries some risk.

The odds of producing an embryo that is disease-free, a perfect match, and capable of initiating a pregnancy are daunting. In January 1999, Lisa Nash produced 12 eggs, 2 of which were healthy matches. She became pregnant, but miscarried. In June she produced only four eggs, one of which was a match, but she did not become pregnant. In September, she produced eight eggs, only one of which was a healthy match, but again she did not become pregnant. Molly was getting sicker and her physician recommended proceeding with a transplant from a nonrelated donor, although the odds that such a transplant would work were virtually nil. The Nashes decided to try a different IVF clinic, one known for being more aggressive. Lisa’s hormone regimen was changed and in December 1999, 24 eggs were retrieved. Only one was a match, but this time she became pregnant. She was confined to bed to prevent a miscarriage. On August 29, 2000, after 52 hours of labor (Lisa resisted a cesarean section because more cord blood could be collected during a vaginal birth), Adam Nash was delivered by C-section. In October 2000, doctors at Fairview-University Hospital in Minneapolis, which specializes in bone marrow transplants for children with Fanconi anemia, successfully transferred tissue from Adam’s umbilical cord into Molly’s body. Molly, by all accounts, is doing very well. She is back at school, or rather a visiting teacher, who must wear a mask during lessons, comes to her home. She takes ballet lessons. Her transplant did not cure her of Fanconi anemia, but merely prevented her from developing leukemia. She is likely to suffer Fanconi’s other complications, particularly cancers of the mouth and neck, but that is far off in the future.

Adam Nash was not unique in being conceived to save a sibling. Ten years earlier, another couple, Abe and Mary Ayala, decided to have Abe’s vasectomy reversed, in the hopes that Mary would become pregnant with a child who could be a bone marrow donor for their daughter, Anissa, aged 17, who had been diagnosed with leukemia. Surprisingly, the reversal worked and Mary, aged 42, became pregnant. Moreover, the baby, Marissa Eve, born on April 3, 1990, turned out to be a compatible donor.

Is using PGD to select an embryo in order to save another child ethical? If yes, are there any situations in which it would not be ethical? If no, are there any situations in which it would be ethical? How do you think the child who was selected in order to save the sibling would answer this question? Is there any difference ethnically between the Nash family scenario and the Ayala family one? Does this scenario and similar ones have any greater implications for the medical community and for society?
At the time, the reaction from medical ethicists was generally negative. Philip Boyle, an associate at the Hastings Center, said, “It’s troublesome, to say the least. It’s outrageous that people would go to this length.” Alexander Capron, professor of law and medicine at the University of Southern California, suggested that having a baby to save another child was ethically unacceptable because it violated the Kantian principle that persons are never to be used solely as a means to another person’s ends. Others, however, challenged the view that Marissa was being used as a means only, or that she was not given the respect due to persons. The crucial thing, they argued, was that her parents and siblings intended to love the new addition to the family as much as her older brother and sister, whether or not she could donate bone marrow. The risk to Marissa was minimal; indeed, if Anissa already had a baby sister with compatible marrow, no one would have questioned using the infant as a donor. Why should the moral situation be different if the choice is to create a child in the hopes that she will be a donor?

Unlike the Ayalas, who thought they had completed their family, the Nashes wanted another child. When they were told that the same technique that could prevent the birth of a child with Fanconi might also identify a compatible donor for Molly, they jumped at the chance. As Mrs. Nash put it, “You could say it was an added perk to have Adam be the right bone marrow type, which would not hurt him in the least and would save Molly’s life. We didn’t have to think twice about it.”

Are there ethical objections to what the Nashes did? Some oppose PGD even for its ordinary use, to prevent the birth of a child with a serious disability. Others do not oppose PGD in principle, but think that it should not be used to save the lives of existing children. One concern is that the parents of fatally ill children will be unable to refuse to go through IVF if it is presented as their only chance for saving their child. Furthermore, not every story of a Fanconi child has the happy ending afforded the Nash family. Some women go through cycle after cycle of IVF, only to fail to produce a compatible embryo, or to suffer repeated miscarriages. It may be argued that this is not a choice that doctors should offer desperate parents, given that the odds of success are relatively low. At the same time, many women choose to undergo the rigors of IVF to have babies. If it is not unethical to give them this choice, is it unethical to give them the chance to save their child’s life, if they are fully informed about the burdens and risks, and the odds of success?

Some ethicists object to the idea of having a baby for “spare parts.” Clearly it would be wrong to create a baby for spare parts if that would be harmful to the child. One could not create a baby for his heart or lungs or even kidney. In what sense has Adam Nash been harmed? He owes his very existence to the fact that he was a perfect match for Molly. Of course, many embryos were discarded and this is considered immoral by those who view preimplantation embryos as tiny children. This, however, is not an objection to using PGD to create donors, but to PGD generally, and indeed to all of IVF.

Finally, many are profoundly disturbed by the possibility of “having babies to spec,” of choosing who will be born based on their genetic characteristics. “If we can screen an embryo for tissue type, won’t we one day screen for eye color or intelligence?” Some ethicists fear that the use of PGD to get compatible donors today will lead to a world in which parents will be able to select their children’s physical, mental, and emotional traits. From one perspective, PGD offers parents of desperately ill children the hope of a miracle. From another, it opens the door to “genetic engineering” and a new eugenics.
Role-playing Guidelines: ELSI Scenarios

You will be assigned to a team of 3-5 students and given an E.L.S.I. scenario. Read through the scenario and discuss the issues raised with your group members. Determine two sides to the situation. Break your scenario group into two sub-groups. Each sub-group will begin to research in preparation to defend both sides of the conflict. At the time of presentation your sub-group will be assigned a side to argue by Robert or Dr. Engelman.

Approximate Timeline:

- **Day One**  Read through scenario. Ash clarifying questions and divide into sub-groups. Begin research.
- **Day Two**  Research day
- **Day Three**  Finalize arguments
- **Day Four**  Present arguments for evaluation

Key Concepts:

You are to use the current state of our scientific understanding to aid in making your case for the proper resolution of the various E.L.S.I. scenarios. This is intended as a difficult exercise but you will be evaluated using the rubric provided. Thoroughness and thoughtfulness will be required for success.
### Categories

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<th>Exceeded</th>
<th>Achieved</th>
<th>Developing</th>
<th>Emerging</th>
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</table>
| **Group Cooperation** | o Accepts ideas of others and able to compromise  
   o All members contribute | o Accepts most ideas w/o negative comments and able to compromise  
   o Some members contribute | o Unwilling to compromise  
   o Few members contribute | o Group does not work together  
   o One person does all the work |
| **Understanding of ELSI conflict** | o All aspects of the ELSI are presented | o Some aspects of the ELSI are presented | o ELSI content is superficially discussed | o ELSI content is not presented |
| **Understanding of State of the Science** | o The science is presented thoroughly  
   o The science is used to strongly support a view of the ELSI conflict  
   o Common misconceptions are cleared | o The science is presented thoroughly  
   o The science is used to somewhat support a view of the ELSI conflict | o The science is presented  
   o The science is used somewhat to support an ELSI viewpoint | o The science is incompletely presented or is presented with misconceptions  
   o The science presented does not provide support for an ELSI viewpoint |
| **Presentation** | o Informative  
   o Engaging  
   o Easily understood | o Informative  
   o Somewhat engaging  
   o Can be understood | o Somewhat informative  
   o Not engaging  
   o Difficult to understand | o Lacks information  
   o Disengaging  
   o Cannot be understood |
| **Research** | o More than three academically acceptable web-based sources are utilized  
   o All sources are cited using APA format | o 2-3 academically acceptable web-based sources are utilized  
   o All sources are cited | o Only 1-2 academically acceptable web-based sources are utilized  
   o Sources are not cited or cited insufficiently | o Only 1 source of information or sources are not academically acceptable  
   o Sources are not cited or are insufficiently cited |