

Teacher Guide: The Bioethics of Gene Therapy

ACTIVITY OVERVIEW

Abstract:

Students read accounts of recent gene therapy trials and consider the ethical implications in each and in continuing gene therapy trials as a whole. Using a bioethical decision-making model, students will state the ethical questions, list relevant facts, identify stakeholders, consider values and develop possible solutions to dilemmas that arise from gene therapy treatments.

Module:

Gene Therapy: Molecular Bandage?

Prior Knowledge Needed:

The basic idea behind gene therapy; viral vectors

Key Concepts:

Bioethics of gene therapy

Materials:

Student Handouts

Appropriate For:

Ages: 12 - 20

USA grades: 7 - 14

Prep Time:

15 minutes

Class Time:

60 minutes or more depending on group and discussion structure

Activity Overview Web Address:

<http://gslc.genetics.utah.edu/teachers/tindex/overview.cfm?id=gtbioethics>

Other activities in the *Gene Therapy: Molecular Bandage?* module can be found at:

<http://gslc.genetics.utah.edu/teachers/tindex/>

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I. PEDAGOGY

A. Learning Objectives

- Students will consider the bioethical issues related to gene therapy.
- Students will learn about hallmark gene therapy trials.
- Students will examine a bioethical issue from the viewpoint of various stakeholders.
- Students will learn about the risks and potential outcomes involved in actual gene therapy trials.

B. Background Information

The overall goal of gene therapy is to restore normal function in cells affected by genetic disorders. The most common method for doing so involves the use of viruses as vectors.

The challenges and risks involved in gene therapy include: delivering the normal gene to an adequate number of the correct types of cells, making sure the new gene is not introduced into the patient's germline, eliciting an immune response to the viral vector, and disrupting the function of other genes if the new gene integrates itself into them. More information about the risks and challenges is available in the online portion of the *Gene Therapy: Molecular Bandage?* module (see *Activity Resources*, page 4).

This activity provides synopses of three hallmark gene therapy clinical trials. One is an example of a success (Ashanti de Silva), one was unsuccessful (Jesse Gelsinger) and the third is a mixture (Rhys Evans). Each raises its own ethical questions while sharing a common one: *Should experimental gene therapy trials continue, given the known risks and uncertain outcomes?* Students will use an ethical decision-making model to examine the trials and their ethical dilemmas (page S-4).

For more information about the therapies described in each scenario see the online portion of the *Gene Therapy: Molecular Bandage?* module (see *Activity Resources*, page 4).

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C. Teaching Strategies

1. Timeline

- One day before activity:
 - Determine which discussion format you would like to use (see *Classroom Implementation*)
 - Make the appropriate number of copies of the case study(s) you will use (pages S-1 through S-3)
 - Make the appropriate number of copies of the Ethical Decision-Making Model (page S-4)
- Day of activity:
 - Divide class into groups, if appropriate
 - Hand out copies of scenarios and Ethical Decision-Making Model (pages S-1 through S-4)
 - Provide time for students to complete the Ethical Decision-Making Model in groups

2. Invitation to Learn

- Watch the film *The Boy in The Plastic Bubble* (1976) - John Travolta plays a teenager who was born without a functioning immune system (Severe Combined Immune Deficiency, or SCID) and must live in a plastic isolation chamber.
- As a class, brainstorm positive and negative aspects of gene therapy.

3. Classroom Implementation

- One case study
 - Choose one case study to work with.
 - Have students read the case study and discuss questions 1-3 on the Ethical Decision-Making Model in pairs or small groups.
 - As a class, decide who the major stakeholders are (i.e. patients, research scientists, biotech companies, other people with the disorder, etc.).
 - Assign students to stakeholder groups.
 - Have each stakeholder group discuss questions 4-6 on the Ethical Decision-Making Model (page S-4) from the perspective of their stakeholder and prepare a short summary of their discussion to share with the class.
- Two or more case studies
 - Choose two or more case studies to work with.
 - Split the class into equal groups per each case study.
 - Have each group complete the Ethical Decision-Making Model (page S-4). They may either break into smaller stakeholder groups, or discuss the various

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stakeholder points-of-view as a whole group.

- Each group should prepare a brief summary of their discussion to share with the rest of the class.
- Jigsaw - student choice
 - Divide the class into three groups.
 - Assign a different case study for each group to read; they will be the “experts” for their assigned case.
 - Have the groups discuss questions 1-2 on the Ethical Decision-Making Model (S-4) and prepare to share their answers with other members of the class.
 - Have students divide into small groups of three with each group containing one member from each of the “expert” groups.
 - Have each “expert” share their case study and answers to questions 1-2 with their new group.
 - Once all the experts have shared their case studies, ask the groups to choose which case is most compelling to them.
 - Direct the groups to discuss questions 3-6 of the Ethical Decision Making Model (page S-4) as they relate to the case they chose and to prepare a short summary of their discussion to share with the rest of the class.

4. Extensions

- The Jesse Gelsinger story lends itself nicely to discussion and/or follow-up research. The investigation following Jesse’s death revealed important questions about:
 - lapses in reporting deaths and adverse reactions in gene therapy trials
 - potential conflicts of interest for researchers who also held stock in biotech companies that were funding the research
 - questions surrounding the experimental design of this particular gene therapy trial
 - questions about Jesse’s fitness to participate immediately before the therapy

More information about the Gelsinger case is available in *Gene Therapy: Molecular Bandage? - Additional Resources* (see *Additional Resources*, page 4).

- Follow up this activity with the *Positions, Beliefs and Values* activity (see *Additional Resources*, page 4).

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5. Adaptations

- Stage a class debate using one of the synopses.
- If groups are struggling with the stakeholder roles, you may want to take some time to discuss the characteristics and attributes of each stakeholder group.
- If short on time, have students read one scenario and fill out the Ethical Decision- Making Model (page S-4) individually.

6. Assessment Suggestions

- Use the students' short summary presentations as an assessment.

II. ADDITIONAL RESOURCES

A. Activity Resources linked from the online Activity Overview at:

<http://gslc.genetics.utah.edu/teachers/tindex/overview.cfm?id=gtbioethics>

- Website: *Gene Therapy: Molecular Bandage?* - extensive information about gene therapy, including information about viral vectors, the associated risks and challenges, and additional resources.
- Article: *If Gene Therapy is the Cure, What is the Disease?* by Arthur L. Caplan, Ph.D (on bioethics.net)
- Film: *The Boy in the Plastic Bubble* (1976) - John Travolta plays a teenager who was born without a functioning immune system (SCID) and must live in a plastic isolation chamber.
- Activity: *Positions, Beliefs and Values* - Students review statements about gene therapy and determine how strongly they agree or disagree with each one. Students also write out the personal belief that leads them to their position.

III. MATERIALS

A. Detailed Materials List

- Copies of gene therapy synopses, one per student or group
- Copies of the Ethical Decision-Making Model, one per student or group
- Any materials necessary for student presentations

B. Materials Preparation Guide

Decide which discussion format and case studies you would like to use; copy the appropriate number of materials to distribute to groups or individual students.

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IV. STANDARDS

A. U.S. National Science Education Standards

Grades 5-8:

- Content Standard F: Science in Personal and Social Perspectives - Science and Technology in Society; scientists and engineers have ethical codes requiring that human subjects involved with research be fully informed about risks and benefits associated with research before the individuals choose to participate.

Grades 9-12:

- Content Standard C: Life Science - The Molecular Basis of Heredity; in all organisms, the instructions for specifying the characteristics of the organism are carried in DNA.
- Content Standard F: Science in Personal and Social Perspectives - Science and Technology in Local, National and Global Challenges; individuals and society must decide on proposals involving new research and the introduction of new technologies into society. Decisions involve assessment of the alternatives, risks, costs and benefits and consideration of who benefits and who suffers, who pays and gains, and what risks are and who bears them. Students should understand the appropriateness and value of basic questions - "What can happen?" - "What are the odds?" - and "How do scientists and engineers know what will happen?"

B. AAAS Benchmarks for Science Literacy

Grades 9-12:

- The Living Environment: Heredity - genes are segments of DNA molecules; inserting, deleting, or substituting DNA segments can alter genes; an altered gene may be passed on to every cell that develops from it; the resulting features may help, harm, or have little or no effect on the offspring's success in its environment.
- The Human Organism: Physical Health - faulty genes can cause body parts or systems to work poorly.
- The Designed World: Health Technology - knowledge of genetics is opening whole new fields of health care.

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C. Utah Secondary Science Core Curriculum

Intended Learning Outcomes for Biology

Students will be able to:

4. Communicate Effectively Using Science Language and Reasoning
 - a. Provide relevant data to support their inferences and conclusions.

Biology (9-12)

Standard 4: Students will understand that genetic information coded in DNA is passed from parents to offspring by sexual and asexual reproduction. The basic structure of DNA is the same in all living things. Changes in DNA may alter genetic expression.

Objective 3: Explain how the structure and replication of DNA are essential to heredity and protein synthesis.

- Research, report, and debate genetic technologies that may improve the quality of life (e.g., genetic engineering, cloning, gene splicing).

V. CREDITS

Activity created by:

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Acknowledgements:

The Ethical Decision Making Model is from:

Campbell C, Donnelly S, Jennings B, and Nolan K. *New Choices, New Responsibilities: Ethical Issues in the Life Sciences*. Briarcliff Manor, N.Y.: Hastings Center, 1990.

The Bioethics of Gene Therapy Case Study One

Ashanti de Silva



Photo: Courtesy of Van de Silva

In September 1990, four-year-old Ashanti de Silva became famous in the scientific and medical communities as the world's first gene therapy patient.

Ashanti was born with adenosine deaminase deficiency (ADA). People with this genetic disorder do not produce an enzyme necessary for immune system function. As a result, their immune systems do not work properly and even mild illnesses, such as the common cold or flu, can become deadly.

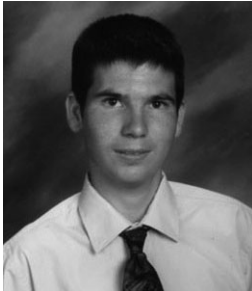
To begin Ashanti's gene therapy, white blood cells were taken from her body and grown in culture. A retroviral vector carrying the ADA gene was then added. The retrovirus infected the dividing cells in the culture and delivered the ADA gene. These white blood cells were then injected back into Ashanti's body where they resumed their normal function. This therapy was very effective in animal trials, but no one knew what the effects would be in a human.

Ashanti's treatment was a success and to this day she has shown no side effects. Her immune system is functioning normally even though only 20-25% of the type of white blood cells used in the gene therapy trial contain the desired gene. In addition, Ashanti has continued taking low doses of the medication commonly prescribed for ADA as a precaution.

The success of this first gene therapy trial bred much optimism that gene therapy would be an effective treatment for many other disorders in the future.

**The Bioethics of Gene Therapy
Case Study Two**

Jesse Gelsinger



A medical study at the University of Pennsylvania took a turn for the worse in September 1999 when Jesse Gelsinger, age 18, died from complications related to a gene therapy he had received as part of an experimental trial. At the time, this was the first known death directly attributable to gene therapy.

Gelsinger was a voluntary participant in the gene therapy trial whose aim was to treat a fatal liver disorder known as ornithine transcarbamylase (OTC). Jesse had a rare, less severe form of the illness that was managed by diet and medication. Despite the required low-protein diet and taking 32 pills each day, Jesse led a normal, active and healthy life. He hoped that his participation in the trial would later help infants and children with the more severe form of the disorder.

The therapy consisted of the OTC gene packaged in an adenovirus vector. The vector was then injected into an artery that leads directly into the liver. Preliminary studies on mice, baboons and monkeys showed success with this approach, with mild (but temporary) side effects. Before this trial no one had injected adenovirus directly into the human bloodstream. Acting on the advice of the University's bioethics expert, the designers of the study decided to use only stable adult carriers of the disease as opposed to sick infants. The study would find the maximum tolerated dose of the adenovirus vector in humans by placing participants in three groups, with each group receiving higher dosages in small increments. Jesse was in the study's last group, hence he received the highest dosage. At the time of Jesse's injection, 17 people had already been treated, one with the higher dosage that Jesse was given. The previous participants had shown mild side effects but were doing well.

Unfortunately, Jesse was not as lucky. Within 24 hours of the injection, Jesse's liver began to show serious signs of distress and he slipped into a coma. Despite the research and medical teams' best efforts, Jesse's condition worsened as one problem cropped up after another. Eventually, Jesse suffered from multiple-organ-system-failure. Four days after the injection, Jesse's body had swelled beyond recognition and there was no sign of brain activity. Jesse's father acted on the advice of the medical team and authorized the withdrawal of life support; Jesse died almost instantly.

The researchers involved in the study determined that there was no evidence of human error and that Jesse's death was the result of an unusual immune response triggered by the adenovirus. Upon investigation, the two governing agencies responsible for overseeing gene therapy trials in the US found that four monkeys in the preliminary studies had a similar reaction to the gene therapy and consequently died. Researchers modified the adenovirus and lowered the dosage in the human trials as a result.

Jesse's death opened a number of questions about gene therapy and halted all gene therapy trials in the US for a while. The agencies found that deaths in other, different trials had not been reported because they were thought not to be directly attributable to the treatment itself. Furthermore, reports of adverse reactions or deaths that were reported were kept confidential upon the request of those filing the reports. Many in the scientific and medical community believe that sharing information about gene therapy trials might prevent something like this from ever happening again.

**The Bioethics of Gene Therapy
Case Study Three**

Rhys Evans



Photo: Courtesy of Jeans for Genes

In 2000, young Rhys Evans received gene therapy to treat his deadly immune system disorder known as X-linked severe combined immunodeficiency disorder (SCID). As a result of this genetic disorder, Rhys did not produce a protein necessary to create the cells of the immune system, leaving his body defenseless.

A retroviral vector was used to deliver the appropriate gene to blood stem cells (from bone marrow) taken from his body. The corrected cells containing the normal gene were then placed back into Rhys' body where it was hoped they would begin normal immune cell production.

For Rhys, the treatment was a success. Two years after receiving the therapy his immune system is functioning properly and there have been no side effects. Rhys was cured by this gene therapy.

Two French boys who underwent the same gene therapy were not as lucky, however. Though all appeared to go well after the therapy was administered, both boys later developed leukemia. Researchers showed that this happened because the newly transferred gene had inserted itself into a bad place, interrupting the function of a gene that helps to regulate the rate at which cells divide. As a result, the cells began to divide out of control, creating the blood cancer, leukemia.

This unfortunate side effect did not come as a total surprise to doctors and researchers. The possibility of the gene stitching itself into the wrong location and causing cancer was acknowledged before the trials began, and the risk calculated to be low. The benefits of this treatment seemed to outweigh the risk. The parents of the young children who participated in the study were informed of this risk prior to the treatment.

These two cases were enough to halt gene therapy trials using this particular approach in France, England and the United States in 2002. Furthermore, the National Institutes of Health in the United States recommended stopping all therapies involving a retrovirus vector. Of the 14 boys who received gene therapy for SCID, all are still alive and doing well; the two who developed leukemia have responded well to treatment.

