



DIVISION OF MEDICAL ETHICS  
HIGH SCHOOL BIOETHICS PROJECT

# CRISPR and Genetic Modification

## Overview

This module aims to build an understanding of the moral and ethical implications of genetic modification, specifically regarding the use of CRISPR technology for germline (heritable) and somatic (non-heritable) genetic editing. The module will incorporate a study of recent scientific discoveries, breakthroughs, and controversies through ethical and conceptual lenses. While CRISPR has a variety of potential applications, this module explores the genetic modification of human DNA and the consequences of these edits.

CRISPR is a technology adapted from a naturally occurring genome editing system in bacteria that is a more accurate, effective, and cost-efficient way to alter DNA than techniques used previously. It allows geneticists and medical researchers to edit parts of the genome by removing, adding, or altering parts of the DNA sequence. What is CRISPR and how does it work? Why have scientists currently called for a moratorium on the clinical use of CRISPR for germline modification?

What is the future of CRISPR, how will it be regulated, and how will it affect the world in which we live? This module will delve into these questions and leave the classroom with a newfound understanding of the ethical implications behind the use of this technology.

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1. Key Terms
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## Learning Outcomes

1. Gain a solid understanding of how CRISPR technology functions
2. Learn the difference between germline and somatic editing
3. Be able to participate in thoughtful discussions regarding the ethical concerns of genetic modification
4. Come to a conclusion about how CRISPR technology should be regulated and/or controlled

## Procedures and Activities

This module is a student-led exploration of the world of genetic modification with a specific focus on germline modification and the recent developments in the scientific community. Students will participate in discussion and group activities to better their understanding of the material and incorporate the viewpoints of others into their own thinking.

# 1. Introduction to the Topic

## Teacher-Directed Class Discussion

### A. What is CRISPR?

CRISPR, or “clustered regularly interspaced short palindromic repeats,” is an innovative technology that allows geneticists to alter the genome by adding, deleting, or changing portions of the DNA sequence. CRISPR has entirely changed the genome engineering sector by providing a cheap and efficient way to alter DNA. The technology’s many potential applications include correcting genetic mutations, treating existing diseases in animals and humans, and enhancing varieties of crops. Its use in humans also poses a number of ethical dilemmas.

### B. How the Technology Works

The basic CRISPR-Cas9 system consists of two molecules that introduce one or more modifications into DNA. The first, Cas9, is an enzyme that acts as a pair of ‘molecular scissors’ that can cut both strands of DNA at a specific location so that pieces of new DNA can then be added, or existing DNA can be removed. A modified version of Cas9 has been developed to only cut one strand of DNA, while another has been developed to bind to DNA without any cut at all. The second molecule, a piece of RNA called guide RNA (gRNA), consists of a small piece of pre-designed RNA sequence (about 20 bases long) located within a longer RNA scaffold. The scaffold binds to DNA and the pre-designed sequence guides Cas9 to the correct location. The guide RNA has RNA bases that are complementary to those of the target DNA sequence. This should mean that the guide RNA will only bind to and deliver Cas9 to the target sequence. When Cas9 cuts the DNA, the cell recognizes that the DNA is damaged and tries to repair it. Scientists thus use the cell’s own DNA repair machinery to introduce changes to one or more genes in the genome.

### C. Why is CRISPR Preferable to Other Technologies?

There are currently several classes of genome editing techniques. These include

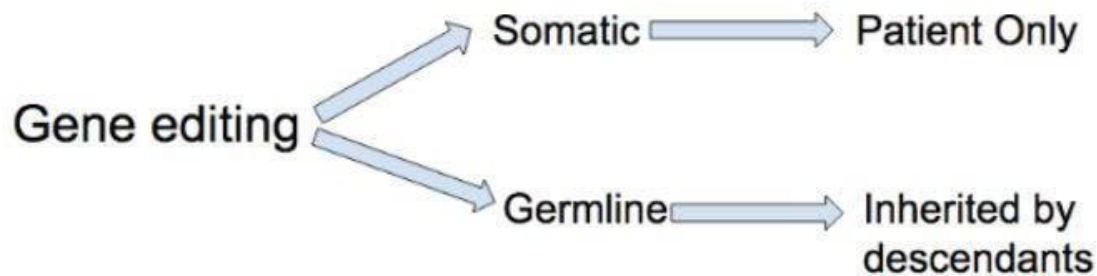
zinc finger nucleases (ZFN), transcription activators like effector nucleases (TALENs), and the CRISPR system. The CRISPR system has entered the picture as a faster, cheaper, and more accurate way of editing DNA in comparison to traditional ZFN and TALENs approaches. CRISPR technology is superior in terms of its design simplicity, engineering feasibility, ability to target multiple locations at once, large-scale library preparation, specificity, efficiency, and cost. CRISPR RNA, for example, is easily designed, while ZFN requires customized proteins for every DNA sequence and TALENs has technical issues with engineering and delivery into cells. Furthermore, the flexibility offered by multiple variants of Cas9 lends the CRISPR approach phenomenal versatility and a large range of potential applications. As a result of CRISPR’s advantages, it has attracted a larger investment of research, time, and resources, which furthers its dominance over other techniques.

### c. Germline Versus Somatic Genetic Editing

Certain diseases appear to be suitable for treatment by gene editing of some of the body’s non-reproductive cells (somatic editing), while other genetic diseases might best be treated by gene editing of the reproductive cells or early embryos (germline editing). There are many differences between somatic and germline intervention; listed here are some of the most prevalent

| <b>Somatic Modifications</b>  | <b>Germline Modifications</b>   |
|---|---|
| Somatic therapies target genes in specific types of cells in an individual: lung cells, skin cells, blood cells, retina, etc. | Germline modification is applied to embryos, sperm, or eggs, and alters the genes in all the resultant person’s cells |
| Non-inheritable and only affects the treated individual   | Passed onto future generations  |
| First somatic trials occurred almost 30 years ago   | Human germline editing of early embryos for research purposes began in 2015   |

|  |  |
|--|--|
| <p>These mutations only show their effects in the cells where they occur</p> | <p>In most cases, germline mutations are 'silent' in the parent organism in which they originally occurred, except in cases when they affect the gamete production</p> |
|--|--|



## 2. Definitions

### Group Activity

Students should find partners and each student should pick three terms from the list below. Each student should then write three sentences using the terms chosen. When completed, partners should switch their papers, correct any errors they see, and return the paper and discuss the results.

#### *Cells*

Cells are the basic building blocks of all living things. The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions. Cells also contain the body's hereditary material and can make copies of themselves.

#### *DNA*

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Almost every cell in a person's body has the same DNA. Most DNA is located in the cell nucleus (nuclear DNA), although a small amount of DNA can be found in the mitochondria (mitochondrial DNA or mtDNA). The information in DNA is stored as a code made up of four chemical bases:

Adenine

(A)

Guanine

(G)

Cytosine

(C)

Thymine

(T)

Human DNA consists of approximately 3 billion bases, 99 percent of which are the same in all people. The specific order of these bases determines the information available for building and maintaining an organism. DNA bases pair up with each other, A with T and C with G, to form units called base pairs.

### *Genes*

Genes are the functional and physical units of heredity passed from parent to offspring. Genes are pieces of DNA that can vary in size from a few hundred DNA bases to more than 2 million bases. Every person has two copies of each gene, one inherited from each parent. Most genes code for a specific protein or segment of protein leading to a particular characteristic or function.

### *Genome*

A genome is an organism's complete set of DNA, including all of its genes. Each genome contains all of the information needed to build and maintain that organism.

### *Genotype*

Genotype refers to the genetic makeup of an organism. It describes an organism's complete set of genes. The term can be used to refer to the alleles, or variant forms of a gene, that are carried by an organism.

### *Phenotype*

Phenotype refers to the observable physical properties of an organism; these include the organism's appearance, development, and behavior. An organism's phenotype is determined by its genotype, which is the set of genes the organism carries, as well as by environmental influences upon these genes.

### *Nucleotides*

Nucleotides are made up of a base, sugar, and phosphate. Each base is attached to a sugar molecule and a phosphate molecule. Nucleotides are arranged in two long strands that form a DNA spiral called a double helix. The structure of the double helix is somewhat like a ladder, with the base pairs forming the ladder's rungs and the sugar and phosphate molecules forming the vertical side pieces of the ladder.

### *RNA*

RNA is the "DNA photocopy" of the cell. When the cell needs to produce a certain

protein, it activates the protein's gene and produces multiple copies of that piece of DNA in the form of messenger RNA, or mRNA. The multiple copies of mRNA are then used to translate the genetic code into protein through the action of the cell's protein manufacturing machinery, the ribosomes. ("mRNA" came into mainstream use during the Covid-19 pandemic when it served as the base for two of the vaccines developed to fight the virus.)

### *A Gene Pool*

Gene pool is the sum of a population's genetic material at a given time. The term is typically used in reference to a population made up of individuals of the same species and includes all genes and combinations of genes in the population.

### *Alleles*

Alleles are any one of two or more genes that may occur alternatively at a given site or locus on a chromosome. They may occur in pairs or there may be multiple alleles affecting the expression of a particular trait. Most traits are determined by more than two alleles, and all genetic traits are the result of the interactions of alleles.

### *Chromosome*

A chromosome is the microscopic threadlike part of the cell that carries hereditary information in the form of genes. 46 chromosomes in 23 pairs are found in each human cell.

### *Eugenics*

Eugenics is the selection of desired heritable characteristics with the goal of improving future generations, typically in reference to humans. The term eugenics was coined in 1883 by British explorer and natural scientist Francis Galton, who, influenced by Charles Darwin's theory of natural selection, advocated a system that would allow "the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable."

### *Mutation*

A mutation is an alteration in the genetic material (genome) of a cell of a living organism or of a virus that is more or less permanent and that can be transmitted to the cell's or the virus's descendants



### *Germline Mutation*

A germline mutation is an alteration in the genetic constitution of the reproductive cells, occurring in the cell divisions that result in sperm and eggs. Germinal mutations may affect a single gene or an entire chromosome. A germinal mutation will affect the progeny of the individual and subsequent generations of that progeny.

### *Somatic Mutation*

A somatic mutation is a genetic alteration acquired by a cell that can be passed to the progeny of the mutated cell in the course of cell division. The mutation affects all cells descended from the mutated cell. However, somatic mutation differs from germline mutation in that germline mutations are inherited, while somatic mutations are limited to the individual.

## **3. Goals and Applications of CRISPR**

### **D. What Are Potential Applications?**

CRISPR-Cas9 has the potential to treat a range of medical conditions directly caused by genetic mutations. The majority of research regarding CRISPR technology is currently conducted in an attempt to treat conditions caused by DNA mutations in a single gene. Cystic fibrosis, hemophilia, and sickle cell disease are examples of damaging and in some cases even life-threatening conditions that are caused by something as simple as a single base letter change from an A to a T. Research is also focusing on the treatment of more complex diseases that are not caused by a single genetic mutation but are instead affected by multiple genes, as well as environmental factors. Diseases such as cancer, heart disease, mental illness, and human immunodeficiency infection (HIV) fall into this category. While research of somatic modification is not a new endeavor, discussion regarding the potential of germline modification has escalated in recent years. Over time, some believe germline modification may even make it possible to completely eliminate genetic diseases, as the offending mutations are removed entirely and indefinitely from the human genome.

### **E. Examples of Diseases that CRISPR May be Able to Treat or Eliminate**

- Diabetes: SOMATIC INTERVENTION

- Researchers are using CRISPR-Cas9 to develop a personalized treatment for genetic forms of diabetes by replacing insulin-producing cells in patients.
  - The risk of transplant rejection is reduced by using the patient's own cells.
  - The disease affects nearly 30 million Americans and the total cost in the United States is estimated to exceed \$300 billion per year.
- Leber Disease: SOMATIC INTERVENTION
  - The world's first in vivo CRISPR study was announced in a July 2019 press release (in vivo means cells don't have to be removed, treated, and reintroduced to a patient).
  - It aims to treat people born with a form of inherited blindness resulting from a point mutation in a gene called CEP290. The treatment involves injections directly into the retina and targets the most common cause of inherited childhood blindness.
- Sickle Cell Disease: SOMATIC INTERVENTION
  - Researchers are working on an experimental gene therapy treatment for sickle cell disease (SCD), and in early 2021 the first clinical trials for a treatment were approved by the FDA.
  - The treatment would consist of using CRISPR-Cas9 to modify stem cells that are isolated from a patient's blood and then later reintroduced to produce healthy levels of fetal hemoglobin.
  - The higher levels of fetal hemoglobin are expected to counteract pain caused by the sickle cell mutation.
  - Approximately 100,000 Americans are affected by SCD, and the total cost of medical care for SCD is estimated to exceed \$1.1 billion per year.

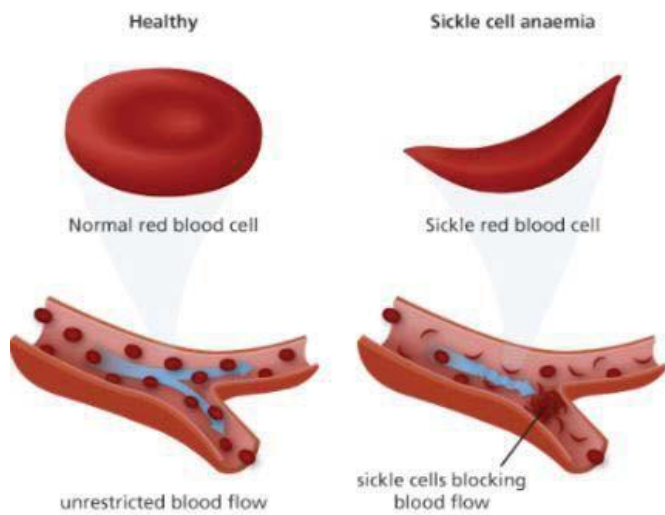


Image Credit: Innovation Toronto

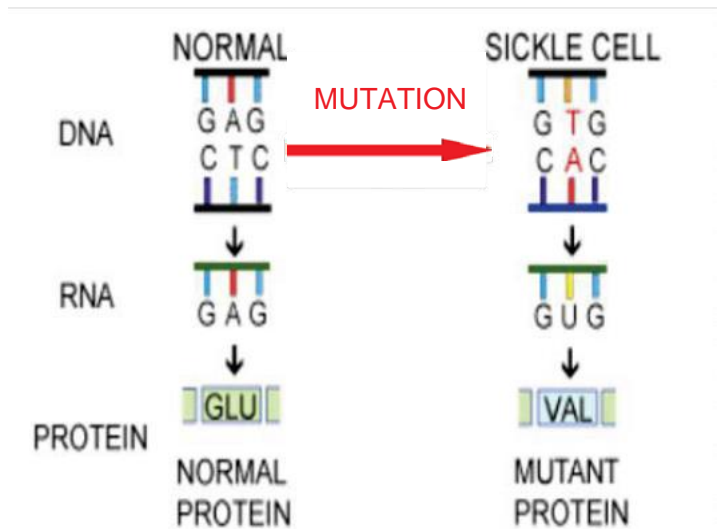


Image Credit: Understanding Evolution

- Duchenne Muscular Dystrophy: GERMLINE INTERVENTION
  - Researchers have demonstrated the ability to use CRISPR-Cas9 to make genetic repairs in cells that allows them to produce dystrophin.
  - Dystrophin is a protein that patients with Duchenne muscular dystrophy (DMD), a genetic disorder, cannot produce.
  - The absence of dystrophin cripples those with DMD and generally leads to heart and respiratory muscle problems.
  - The annual U.S. costs for DMD are estimated to be in excess of \$350 million per year.

## F. Genetic Modification of Embryos

When gene editing is used in embryos, or in gametes (sperm or eggs), it is called germline modification. Also known as “inheritable genetic modification” or “gene editing for reproduction,” these alterations would affect every cell of the person who developed from that gamete or embryo and would be inherited by all future descendants. Assuming there is widespread adoption of the technology, it is possible that the genetic makeup of entire generations could permanently be altered. There is broad agreement among many scientists, ethicists, policymakers, and the public that although germline editing has enormous promise, its use should be restricted to research until the safety of the technology has improved and the

ethical issues have been addressed. Scientists have concerns about the possibility of permanent harm to genetically modified individuals and their descendants as well as concerns about exacerbating social inequality and conflict. The clinical use of germline modification is prohibited in more than 40 countries and by an international treaty of the Council of Europe. Despite this prohibition, in November 2018, a Chinese scientist named He Jiankui announced he had edited the genes of two embryos that were subsequently implanted and resulted in the birth of twin baby girls. This experiment has been widely condemned both in China and around the world. NIH director Francis Collins asserts that He's work "represents a deeply disturbing willingness by Dr. He and his team to flout international ethical norms." Arthur Caplan, a bioethicist at NYU Grossman School of Medicine, notes that "the state of gene editing does not support this first leap into human germline engineering. What's more, the manner in which it was done merits condemnation as an ethical fiasco." The Scientific Ethics Committee of the Academic Divisions of the Chinese Academy of Sciences posted a statement declaring their opposition to any clinical use of genome editing on human embryos, noting that "the theory is not reliable, the technology is deficient, the risks are uncontrollable, and ethics and regulations prohibit the action." The Chinese Academy of Medical Sciences published a correspondence in the *Lancet* stating that it is "opposed to any clinical operation of human embryo genome editing for reproductive purposes." Ren-zong Qiu, an eminent Chinese bioethicist, described He's research as "a practice with the least degree of ethical justifiability and acceptability." This development has resulted in enormous publicity regarding germline modification and has prompted a social debate about the use and governance of the technology.

### G. Enhancement

Recent advances have raised the possibility that genome editing could one day be used for genetic enhancements. Thus, the question has been raised anew as to whether enhancements should be regulated or prohibited. Enhancement has been variously defined as "boosting our capabilities beyond the species-typical level or statistically normal range of functioning" and "a non-therapeutic intervention intended to improve or extend a human trait." Existing controversial non-genetic enhancements include the use of prohibited steroids by athletes. CRISPR may one day enable germline edits to allow for enhancements in traits such as intelligence, resistance to disease, life expectancy, and physical strength for individuals and their descendants. While all of these traits likely involve a combination of multiple genes

and environmental factors that may never be properly understood, there is growing concern that CRISPR may one day make enhancements possible. In 2016, a Pew study of surveys of more than 4,000 individuals revealed anxiety about enhancement through genome editing as well as concerns about enhancement by mechanical and transplant-related means. A public debate about the safety, ethics, and desirability of germline editing is currently underway around the world, with enhancements generally seen as outside the realm of acceptability based on current societal norms, irrespective of how the science develops.

## **4. Problems with the Technology**

### **H. Aspects that Affect CRISPR's Efficiency and Specificity**

There are many technological issues to be overcome before germline editing with CRISPR is considered safe enough to use in germline editing. These include issues with:

- Accurate target site selection
- Guide RNA design
- Off-target effects
- Homology-directed repair
- Method of delivery

CRISPR-Cas9 gene editing typically relies on the Cas9 enzyme to cut DNA at a particular target site. The cell then attempts to repair this break using a cell's own DNA repair mechanisms (homologous repair). However, this cell repair mechanism is not always efficient, and sometimes segments of DNA will be deleted or rearranged, or DNA bases from elsewhere will become incorporated into the gene. Researchers are experimenting with ways to increase repair efficiency, and some versions of Cas9 just bind to DNA without cutting it while a single base is changed. CRISPR can also be used to generate small deletions to knock out a gene's function; however, researchers have found that occasionally larger than expected deletions occur. No experiments yet reported have had error-free results. Although CRISPR is very efficient at disabling genes, there are still technical issues associated with the repair or replacement of defective ones to be resolved. Due to the possibility of off-target effects (unwanted edits in the wrong place) and mosaicism (when some cells carry the edit but others do not), safety is a major concern. Enormous improvements continue to be made with CRISPR, but it must be kept in mind that there are still significant technical hurdles to be overcome before germline editing is safe enough to be used in clinical settings, not to mention the ethical and social issues yet to be resolved.

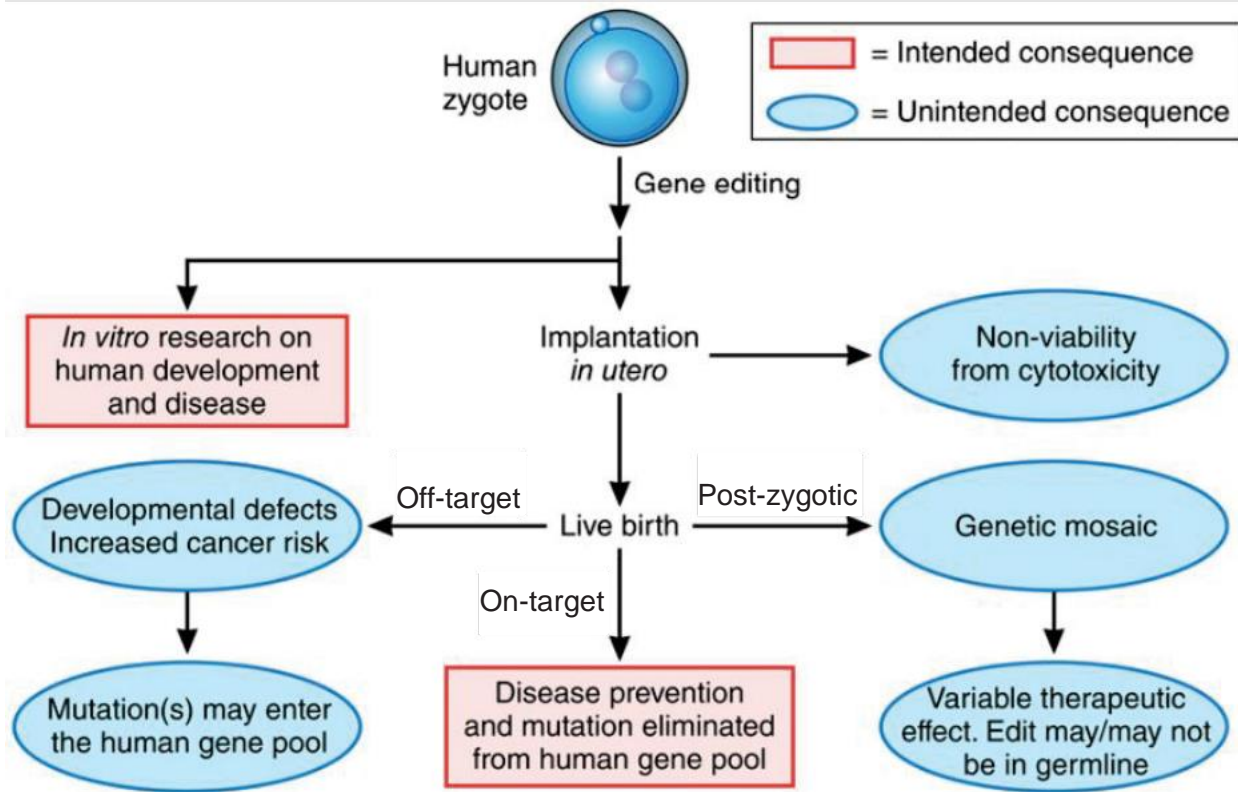


Image Credit: Semantic Scholar

## 5. Ethical Concerns

Beauchamp and Childress describe the four core ethical principles of bioethics as autonomy, beneficence, non-maleficence and justice. These are key principles that should be considered when thinking about the ethical issues associated with germline editing. The ‘autonomy’ principle derives from the ethical principle of human dignity and freedom. It follows from this principle that patients should not be treated without their informed consent or the informed consent of parents/surrogate decision-makers. The principle of ‘beneficence’ requires that what is proposed should result in a positive outcome or benefit, while the principle of ‘non maleficence’ requires an obligation to avoid bad outcomes or harm. Essentially this means that there must be a balancing of the benefits, costs, and risks of any action with an attempt to maximize benefits and minimize harm.

Finally the concept of ‘justice’ relates to whether individuals have a right to a fair minimum level of health care and whether resources are allocated equitably.

A report in May 2019 by a panel of government-appointed experts in Germany attempted to summarize the ethical issues that arise in intervening in the human genome according to these principles. Some of the questions they raised are listed below.

Autonomy/Human Dignity/Freedom:

Does germline intervention remove the dignity of future generations by altering their genome without their consent? On the other hand, would the renunciation of germline intervention violate the dignity of future generations even more because it could have spared many individuals severe suffering?

Should the human species genome itself be the object of the protection of human dignity, or should that be reserved to individuals?

How should the ethical concept of freedom of individuals be considered, including the freedom of scientists to conduct research, the freedom of doctors to advise patients, the freedom of parents to choose to have children free of heritable diseases, and the freedom of those future children whose way of life has been affected by their parents’ choices?

## Beneficence and Non-Maleficence:

The ethical concepts of beneficence and non-maleficence require a benefit-risk analysis, but how can this be achieved given the differing perspectives of members of society? How can it be achieved given the scientific uncertainties inherent in CRISPR technology and the inability to foresee all future consequences of the alterations to genes?

## Justice:

Will germline interventions advance or hinder the principle of political and social justice? Can a sufficient number of individuals from across society be involved in the decision-making on germline interventions and to whom will the technology ultimately be available? Will the cost mean that only the wealthy can access this potentially revolutionary therapy?

After outlining the ethical principles and issues to be considered, the German panel then posed the question of whether, assuming technical deficiencies are overcome by research at some time in the future, clinical trials leading to the birth of genetically modified humans will ever be ethically justified. They discussed three categories of germline editing:

### Single Gene Inheritable Diseases:

They considered a hypothetical case in which both parents are affected by cystic fibrosis and wish to have a child together. Germline intervention would have to be applied to only one gene (a monogenic hereditary disease of which there are many thousands). They concluded that, assuming the safety and efficacy of the technology, “the ethical concepts of the protection of life (dignity), of freedom and of



beneficence suggest for some a duty to permit such interventions and considerations of non-maleficence and justice do not provide any substantial arguments against the interventions.”

### Polygenic Inheritable Diseases:

They next considered cases where diseases such as breast and ovarian cancer are caused by several genes (polygenic) or by combinations of genes and environmental factors (multifactorial) where risks could potentially be reduced by germline editing but not completely avoided. They concluded that in their view there were ethical arguments for and against intervention in these types of cases, particularly as the benefits are less certain and the risks of editing multiple genes much greater than for single gene diseases.

### Enhancements:

Finally, they considered the ethical case of enhancements, and concluded that they would be ethically impermissible if directed by the state (violating human dignity) and impermissible under most circumstances if decided upon by parents (impairs freedom of child being edited and creates justice concerns because of disruptions to human society and inequity in access to enhancement).

Editing the genes of human embryos to create genetically modified people thus raises myriad safety, social, ethical, and political concerns. Listed here are questions created to facilitate a thoughtful discussion about the ethics of genetic modification.

### **A. Ethical and Legal Concerns**

Do we have the right to alter the genome of future generations?

How do we deal with the fact that regulations on germline editing will eventually differ from country to country and CRISPR tourism may occur with U.S. citizens traveling to other countries for treatment and vice versa?

Can we ever obtain true informed consent for germline therapy when the patients affected by the edits are the embryo and future generations?

Can we ever obtain true informed consent from prospective parents as long as the risks of germline therapy are difficult to fully quantify?

## **B. Religious Objections**

Many have moral and religious objections to the use of human embryos for research and also object to the alteration of the genetic makeup of future descendants.

Could genetic engineers be seen as adopting the role of God.

Might the use of genetic editing of germ cells be seen as interfering with the development of the soul?

### **C. Unintended Consequences**

Would the editing of certain diseases or disabilities lead to stigmatization of people who are living with those conditions?

What if seemingly safe genetic changes cause unforeseen harm?

### **D. Regulation/Control**

Who should decide which diseases or disabilities can or should be edited? What are the standards for safety as scientists develop these tools?

Will genome editing, even for therapeutic uses, inevitably result in a slippery slope to non-therapeutic and enhancement uses?

### **E. Economic Disparity**

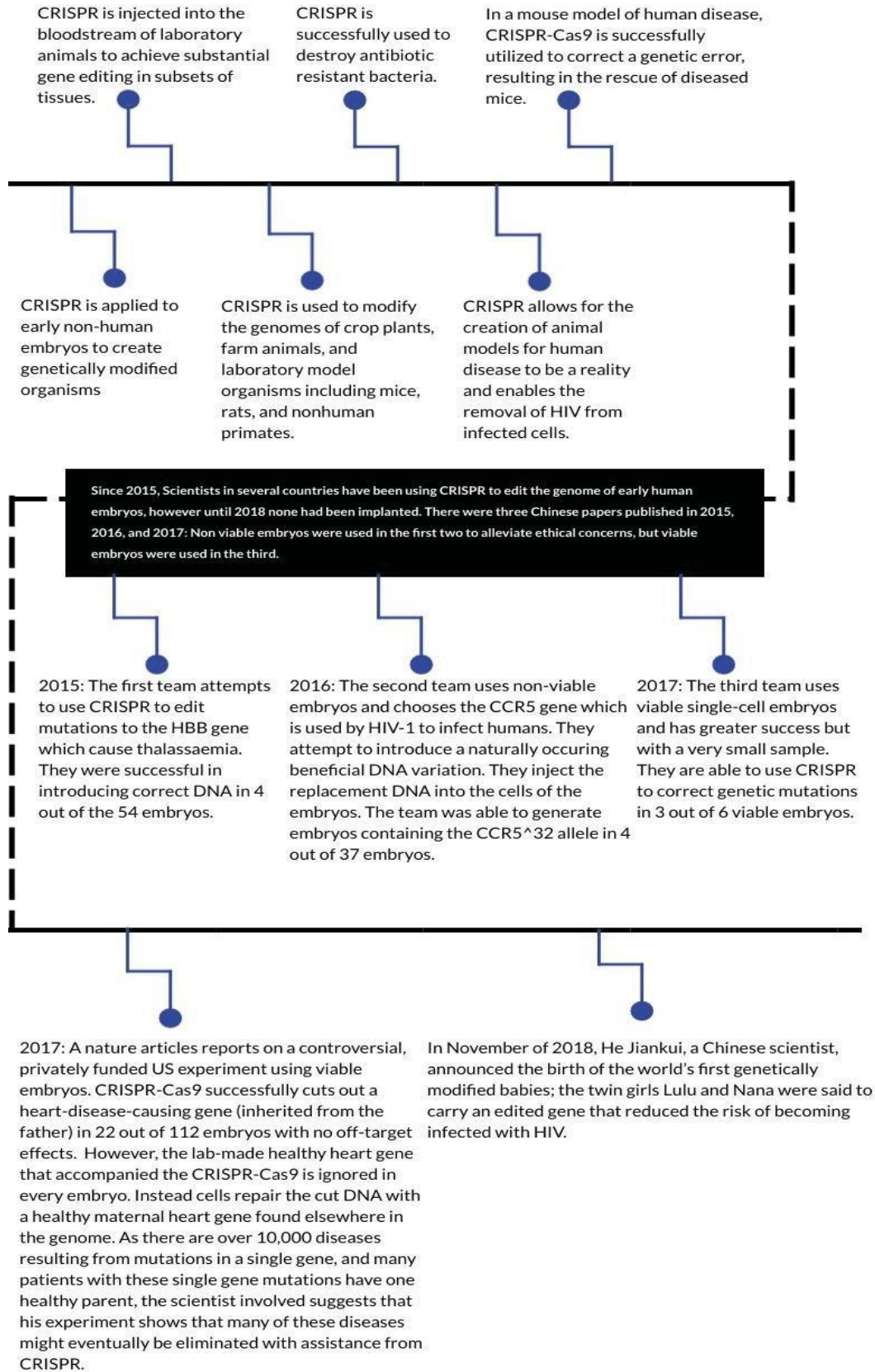
A 2018 Pew Research survey found that “a majority of Americans (58%) believe gene editing will very likely lead to increased inequality because it will only be available to the wealthy.”

How do we prevent genome editing from being accessible only to the wealthy and increasing existing disparities in access to health care and other interventions?

How do we prevent germline editing from creating classes of individuals defined by the quality of their engineered genomes?

## **6. Recent Developments**

## a. How has CRISPR-Cas9 Already Been Used: A Timeline



## b. Governance of the Newfound Technology

The National Institutes of Health (NIH) has a policy that states it will not fund the research of gene-editing technologies in human embryos. It states that “[t]he concept of altering the human germline in embryos for clinical purposes has been debated over many years from many different perspectives, and has been viewed almost universally as a line that should not be crossed.” Furthermore, there are strict guidelines for which research of somatic modification must adhere to in order to receive and maintain funding. According to the report *Human Genome Editing: Science, Ethics, and Governance*, there are 7 Overarching Principles for Research on and Clinical Applications of Human Gene Editing:

|                         |  |
|-------------------------|--|
| 1. Promoting well-being | “The principle of promoting well-being supports providing benefit and preventing harm to those affected, often referred to in the bioethics literature as the principles of beneficence and nonmaleficence.” |
| 2. Transparency         | “The principle of transparency requires openness and sharing of information in ways that are accessible and understandable to stakeholders.”   |
| 3. Due care             | “The principle of due care for patients enrolled in research studies or receiving clinical care requires proceeding carefully and deliberately, and only when supported by sufficient and robust evidence.”  |
| 4. Responsible science  | “The principle of responsible science underpins adherence to the highest standards of research, from bench to bedside, in accordance with international and professional norms.”                             |

|                              |  |
|------------------------------|--|
| 5. Respect for persons       | “The principle of respect for persons requires recognition of the personal dignity of all individuals, acknowledgment of the centrality of personal choice, and respect for individual decisions. All people have equal moral value, regardless of their genetic qualities.” |
| 6. Fairness                  | “The principle of fairness requires that like cases be treated alike, and that risks and benefits be equitably distributed (distributive justice).”  |
| 7. Transnational cooperation | “The principle of transnational corporation supports a commitment to collaborative approaches to research and governance while respecting different cultural contexts.”  |

### **c. First Use of CRISPR Technology to Create Genetically Modified People**

In November 2018, Chinese researcher He Jiankui shocked the world when he announced that he had created the world's first genetically modified people. He claimed that he utilized CRISPR technology to alter the CCR5 gene in a set of twins in an attempt to provide immunity to HIV.

### **Teacher-Directed Class Discussion**

Do you believe He Jiankui's actions were justified? Explain why or why not.

### **d. Call for Moratorium on the Clinical use of Germline Editing**

Partly in response to He Jiankui's shocking announcement, 18 of the top scientists from around the world have called for a moratorium on the clinical use of germline modification. Scientists have defined the moratorium as a number of years where germline modification intended to result in pregnancy would be prohibited. Scientists have specified that during the proposed moratorium, the distinction between a genetic correction and a genetic enhancement would be further explored and debated. Scientists have defined a correction as an edit that tackles a rare mutation strictly for therapeutic medical purposes, while an enhancement improves an individual's "memory or muscles, or even to confer entirely new biological functions, such as the ability to see infrared light or break down certain toxins." The proposed moratorium comes as an alternative to the existing ethical rules surrounding gene editing that have proven to be insufficient in preventing violations and unethical uses of the technology. Some believe that a moratorium is the only way to ethically move forward in terms of establishing regulation and governance of the technology, yet others believe that additional regulation will be insufficient. Concerns include the idea that a moratorium may not prevent individuals from pursuing germline modification, the notion that it may be difficult to lift the moratorium when the time comes, and the possibility that the moratorium will not be universally accepted. Many scientists have expressed the need for enforcement of existing regulations as an alternative or in addition to establishing a moratorium. Scientists have proposed stopping scientific journals from publishing work that violates ethical guidelines and preventing science deemed unethical from receiving research funding.

## **Group Activity**

Have students form small groups and discuss whether or not they believe a moratorium is currently the best route for germline modification. Make sure each student defends their opinion with formulated reasoning. If students get stuck, ask these questions as kickstarters to discussion: What are the benefits and disadvantages of a moratorium? Is a moratorium enough to solve the complex issue at hand? What would happen after the moratorium? How long should the moratorium last? What if certain countries don't agree to a moratorium? If students believe a moratorium is not the best route, what would be an alternative?

### **e. Formal Responses to He Jiankui's Unethical Experiment**

In March 2019, the World Health Organization (WHO) announced a new expert advisory committee to develop global standards for the governance and oversight of human genome editing. The committee will solicit views of a broad group of stakeholders “including patient groups, civil society, ethicists, and social scientists” and will report in two years. The committee agreed that clinical applications of germline editing should not proceed at this time.

In May 2019, the U.S. National Academy of Medicine, the U.S. National Academy of Sciences, and the Royal Society of the UK convened an international commission to study the clinical use of germline editing. The commission issued a report in spring 2020, “Heritable Human Genome Editing.” It covers scientific, societal and ethical issues, identifies protocols for evaluating off target effects and mosaicism, designs protocols for patient consent and ethics approvals, and assesses mechanisms for long-term monitoring of children born with edited genomes.

In July 2019, a bipartisan resolution calling for international ethical standards in genome editing was introduced into the U.S. Senate. The resolution recognized “that the question of whether to proceed with heritable genome editing touches on all of humanity.” It criticized He's experiment without naming him, expressed support for the international commission on germline editing, and called on the secretary of state to work with other nations and international organizations on the ethical use of genome edited human embryos.



## **f. Rogue Scientists?**

Although there is much debate over whether there should be a moratorium on the clinical use of germline modification and formal global reviews have begun on clinical germline editing, a scary thought may be: What if it doesn't matter? What if scientists just proceed anyway? On June 13, 2019, it was reported that Russian biologist Denis Rebrikov had requested permission from the Russian government to edit the same CCR5 gene as He Jiankui targeted in an attempt to create more CRISPR-edited babies. Rebrikov claimed that his technique would “offer greater benefits, pose fewer risks, and be more ethically acceptable to the public.” The Russian government said such the use of gene editing technology on embryos is “premature.” When confronted with the fact that many would consider him to be a second He Jiankui, Rebrikov explained that he would only do so if he's sure of the safety. “I think I'm crazy enough to do it,” he says.

## **7. Concluding Assignment**

### **Individual Activity**

Students should compose a written reflection regarding what they have learned and their opinions about the ethical concerns of CRISPR technology. Their reflections should incorporate a decision about whether CRISPR technology should be allowed to be used for somatic and/or germline modification and a proposal for how the technology could be governed.

## **8. References and Additional Resources**

### **Additional Resources**

- He Jiankui describes his experiment:
  - <https://www.youtube.com/watch?v=th0vnOmFltc&app=desktop>
- Broad overview of CRISPR starting at 3:26:
  - <https://www.youtube.com/watch?v=jAhjPd4uNFY>

- Interactive overview of CRISPR technology
  - <http://media.hhmi.org/biointeractive/click/CRISPR/>

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## **Acknowledgments**

This module was developed and written by Lara Hersch, under the supervision of Kelly McBride Folkers. Maya Grunschlag updated the content in July 2021, under the supervision of Lisa Kearns.



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