Mini-lesson

Claims of CRISPR being used to edit genomes of twin girls born in 2018

In November 2018, news reports began swirling about a scientist's claims that two children had been born with genes that had been edited in the embryonic stage. While screening embryos for certain genetic traits has been possible since the 1990s via a technique called preimplantation genetic diagnosis (PGD), tools to directly alter DNA are a more recent development. Genome editing allows scientists to make changes to specific "target" sites in the genome – almost like using molecular surgical tools to alter individual sections of DNA. One of the tools for performing genome editing, known as "CRISPR" (pronounced like the word "crisper"), has generated the most excitement due to its efficiency and ease of use.

Genome editing tools, including CRISPR, have been used in clinical studies to edit somatic cells in adults and children to treat diseases. Based on studies in other animals, researchers knew that editing human embryos was technically feasible, but not without risks. Since 2015, researchers in several laboratories around the world have reported that they have edited the genomes of embryos but stated that they had not implanted those embryos into any person's womb. The current report is the first one of human beings being born with their DNA purposely altered in a laboratory to possess certain traits (rather than embryos with certain genetic traits being selected for implantation)[1]. pgEd has developed this mini-lesson as a supplement to our lesson plan on genome editing to help teachers discuss this developing story with their students. **The goal of this mini-lesson is to encourage students to think critically about the**

[1] In 2016, an American clinic claimed to have performed mitochondrial replacement therapy (MRT) in Mexico for a Jordanian couple. In MRT, an egg's mitochondria (the "powerhouses" of cells that contain a small amount of DNA) are replaced with mitochondria from a donor egg, with the goal of treating diseases that result from genetic variants in mitochondrial DNA. Unlike the use of CRISPR to edit an embryo's genome, MRT does not involve specifically altering a DNA sequence, but replacing mitochondria does result in genetic changes that can be passed on to future generations. For more about MRT and the 2016 news story, see pgEd's blogpost "In the News: First report of baby born with mitochondrial replacement."

information they are hearing in the news, as the facts about what happened continue to emerge.

What is the story behind these headlines?

Dr. Jiankui He of Southern University of Science and Technology in Shenzhen, China, said that in an attempt to confer immunity to HIV infection, he genetically modified the CCR5 gene in human embryos created via in vitro fertilization (IVF). The CCR5 gene produces a protein that sits on the surface of cells in our body. HIV viruses often (though not always) use the CCR5 protein as a way to recognize and then enter cells. Dr. He altered the gene with the goal of closing this path of infection. Edited embryos were then transferred to the mother, who gave birth to twins Lulu and Nana (these may not be their real names).

News reports of these claims took many people by surprise. Over the past several years, various international meetings and scientific academies, including those of the United States and United Kingdom, have generally recommended that gene editing in embryos with the intention of a child being born should not be carried out at this time. Such an application is also illegal in many countries, including Australia, Canada, and most countries in the European Union, and is against government-issued regulations (which carry the force of law) in others, including China. While no laws in the US explicitly prohibits this procedure, the US Congress bars the Food and Drug Administration (FDA) from considering any application that involves modifying an embryo's genome (FDA approval is required before researchers can begin any clinical investigation).

This case brings attention to many profound ethical questions about potential applications of genome editing in humans. As this story has unfolded in the media, the apparent departure from the accepted process around reviewing, authorizing, and conducting medical research has also drawn particular scrutiny. Lingering questions include:

1. Should genome editing be allowed in embryos, given that the genetic changes, along with any errors in the process, will be passed on to their biological children?
2. Should genome editing only be used in cases of medical necessity (e.g., to treat a disease) or also for purposes of "enhancement?"
3. Will Lulu and Nana experience long-term health effects or unintended consequences because of the edits?
4. Did the informed consent process allow the children's parents to be fully informed about what the experimental procedure involved?

In considering this case, it is important to note that as of February 2019, Dr. He's claims have not been independently verified, nor has his work been published in a peer-reviewed scientific journal.

What does this mini-lesson cover?

This mini-lesson explores a range of topics (e.g., HIV, public health, informed consent) that impact this story, giving students a sense of the complexity of this case, a historical perspective for examining what happened, and a reminder that at the heart of this story are the two girls and their parents. They are asked to **focus on understanding the various dimensions of this case**, not to draw a moral conclusion. As described below, students are given two sources to analyze and discuss. The first is a news article that the whole class will read to get an overview of the birth of twin girls with genetic modifications. For the second, students in groups will receive either a news article or document that provides background knowledge helpful in understanding the news article and, more importantly, reminds students that there are many unknowns and dimensions to this story. As students read, analyze, and then share back to the group, they will start to stitch together the many facts and perspectives that illustrate the complexity of this new development.

Discussion and handouts

This lesson requires articles to be printed and distributed to students. Teachers begin by describing the basics of the editing experiment, using the first paragraph in this mini-lesson if helpful. Students may need some reminders about somatic and germline cells, as well as a quick primer about CRISPR. pgEd has an extensive lesson plan on CRISPR, but if pressed for time, a short video such as this one from *Stat News* will give students the conceptual basics.

Arrange students in groups of three, and hand out printed copies of the following to each group:

- "Why are Scientists so Upset About the First Crispr Babies?" (*New York Times*) – one copy per group (or one per student if preferred).
- a supplemental article/document (listed below). Note: each group will receive a different source; these sources vary in complexity.
- the two-page student worksheet – one per group.

The groups may need approximately 20-35 minutes to discuss and take notes on the two articles. Student groups become "experts" on their source document and will share their interpretations with the class. We recommend that the articles listed below be discussed in the order in which they are listed. This is because the topics, while they

don't tell a linear story, are connected and build on each other in a logical progression. Teachers may facilitate conversation by asking students to provide more details or clarification and to separate facts from opinion. Alternatively, teachers may organize the classroom into a more formal "jigsaw" or "fishbowl" discussion.

Supplemental sources:

1. What is the difference between germline and somatic cells? adapted from pgEd materials.
2. "The Growing Threat of China's HIV Epidemic" from *The Lancet*, 2017.
3. "I am the Berlin Patient," by Timothy Ray Brown in *AIDS Research and Human Retroviruses*, 2015. (Teacher note: This story is a well-known case, but one of only two such examples so far, and there are some strains of HIV that can infect people who have the genetic profile described in this article.)
4. "What Questions Should I Ask if Offered a Clinical Trial?" from *Clinical Research Trials and You*, National Institutes of Health.
5. "Elements of Informed Consent (voluntarism, information disclosure, decision making capacity)" from "Informed consent in clinical research: revisiting few concepts and areas," *Journal of Clinical Perspectives*, 2013; and the Nuremberg Code from 1949, via the National Institutes of Health. (Teacher note: Both of these pieces should be given to the group assigned this topic.)
6. "First Gene Therapy for a Genetic Disorder Gets Expert Endorsement" from *NPR*, 2017.
7. Dr. He's consent form for research experiment (use pages 1-4). Originally found on Dr. He's lab website, it had since been taken down, but is archived on the web. It is presumably an English translation of the Chinese original.
8. "Criteria for Heritable Germline Editing" from the National Academies, 2017.

The following news articles specifically outline some of the social and ethical questions. If time and class size allow, teachers may want to give these to a group or use them to guide and scaffold some of the discussion.

9. "Beyond safety questions, gene editing will force us to deal with a moral quandary" from *Stat News*, 2018.
10. "Should you edit your children's genes?" from *Nature*, 2016.

Questions

Teachers may want to format these discussion questions as handouts or a slide and have them ready to prompt discussion.

- What is the function of CCR5, and why was it chosen for this experiment? Would you consider the editing of CCR5 to be a medical treatment or an enhancement?
- The researchers referred to this experiment – modifying a gene at the embryo stage, creating a permanent and heritable change in the twins – as an "HIV vaccine." How would you describe the experiment based on what you know about hypotheses, controls, etc.?
- What are 3 questions you'd like to ask Dr. He about this experiment? What questions would you pose to a doctor, an ethicist, and a religious leader?
- Describe the concerns for the health and safety of the twins. What is the difference between altering the DNA of an adult versus the DNA of an embryo?

Facilitating a highly charged, emerging news story

Teachers frequently deal with questions and comments that may be well intentioned, but play into stereotypes about certain people, countries or professions. A few of these issues may arise with this story. It may be helpful to remind students of your classroom norms, and that this lesson is meant to look closely at the facts that are known. This is a chance to practice the skill of avoiding speculation in the absence of data. Familiarity with the issues around recognizing and addressing implicit bias may be helpful for teachers (see Scientific American's "How to Think about Implicit Bias" for more), and being ready to field questions and statements that encourage critical thinking will help keep students focused on the task – building a base of knowledge and widening their perspective on germline editing in humans.

We caution anyone using this lesson to reinforce with students that the details of the story are incomplete. It's a great teaching opportunity to help students look for facts, opinions and speculation in the news, and analyze those points accordingly. The parents of the twins have not spoken out about their experience. The genetic status and current health of the twins has not been independently verified. Experts continue to debate the ethics and legality of the research process that appears to have taken place. The scientific community is reflecting on and debating the merits and weaknesses of their own thinking, policies, and recommendations on genetic modification. Typically, scientists publish their work – everything from the materials and methods, results (data), discussion and conclusions – after it had been reviewed by a group of other scientists with expertise to evaluate the scientific merit of the experiments and results (though it is common, even encouraged, for scientists to share their unpublished work at academic conferences to solicit feedback from peers). As of February 2019, Dr. He's work has not been published, and there has been no public acknowledgement that his work is under review (though papers submitted to journals for review are kept confidential, and researchers are under no obligations to reveal whether they have made submissions to any journal). Finally, while students discuss the science and ethics of this case, they should keep in mind that there are real human beings at the center of the story. All of the news stories and debates may someday be seen by the twin girls as

they learn about how they came into the world and the controversy surrounding their births.

Expanding the scientific discussion on the CCR5 gene

In the absence of a peer-reviewed scientific paper, some people are relying on Dr. He's presentation slides at the second International Summit on Human Genome Editing (which took place two days after the news story broke) to understand the details of the changes he claimed to have made to the CCR5 genes of the twins. Based on what Dr. He presented, Dr. Sean Ryder at UMass Medical School created some images that show what these changes supposedly look like, and shared the image on his Twitter feed (students should be cautioned again that Dr. He's results have not been independently validated). The top of the diagram illustrates the well-understood variant in CCR5 (a deletion of 32 DNA letters). It then shows how the changes that might have been put in the twins are different from the known variant. Essentially, the experiment may have created what could be called "variants of unknown significance" or "VUS," a term describing genetic changes where the impact is not understood. Teachers may choose to show this image to students alongside the many caveats we mention here. A more detailed discussion about CCR5's function can be found in the article "Baby gene edits could affect a range of traits," *Nature*, 2018.

pgEd has a number of resources for teachers looking to expand the conversation in this mini-lesson, including lesson plans such as "Genome editing and CRISPR," "History, eugenics and genetics," and the mini-lesson "Sickle cell disease and genetic engineering."

Birth of CRISPR-edited twins

STUDENT HANDOUT

Name: _____ Date: _____

From the Q and A article in the *New York Times*, list 3 facts from the article and list 3 questions you have about this experiment based on the article.

Facts you found in the article:

1.

2.

3.

Questions you have after reading the article:

1.

2.

3.

Birth of CRISPR-edited twins

STUDENT HANDOUT

Name: _____ Date: _____

Read and analyze your group's document. Take notes and be prepared to share your observations with the class.

Questions and Key Points ------- Supporting details and notes

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Summary: