VIDEO TRANSCRIPT

Genome Editing and CRISPR

Link to video.

Slide 1

This PGED lesson gives an overview of the rapidly evolving field of genome editing and one of its newest technologies called CRISPR. Our aim is to examine how advances in our ability to change genomes might impact individuals and society.

Slide 2

Before delving into the presentation, we like to pause to allow people to reflect on a few questions that we will be addressing. Here we explore the following scenario:

Imagine you've been offered a deal from a genomics company. You can get a free genome sequence – an analysis of all your DNA that includes a report of your ancestry, traits and a medical profile. The medical profile tells you about diseases for which you have a low risk of getting, and also those you have a high risk of getting.

Are you interested? Why or why not?

You may want to pause here to think about your own answer to this question.

Those that answer "yes" typically share ideas related to taking steps to prevent or seek early treatment for a

potential health condition. Others may suggest that even if they learned of conditions without a current treatment, they could choose to become active in clinical trials or advocacy work.

Those that answer "no" frequently mention concerns related to privacy and discrimination, such as: who will have access to this information and what can they do with it? Others point to the emotional burden of learning about one's genetic information as a reason to not participate. An often-mentioned example is learning about one's risk for Alzheimer's: a disease for which currently no treatment exists.

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In the previous scenario we focused on genetic analysis, or 'reading' a person's DNA code. In this scenario we take it one step further and we consider the, for now, hypothetical scenario of modifying or changing someone's DNA code.

For the first 100 volunteers, the company is offering to "correct" several of the disease-related genes found by the analysis. Imagine this were a very new procedure approved by the government for safety, but without a great deal of long-term study.

Would you volunteer for this added service?

Pause here to think about your own answer to this question.

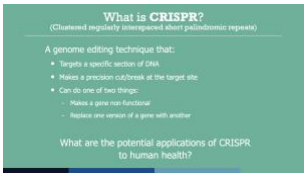
Typically, we hear concerns about volunteering for this service with regards to how safe the procedure is and whether the 'correcting' of a certain disease-related gene might have unanticipated consequences. Some people say

they would do it depending on how serious the potential disease is. Others question the idea of 'correcting' - after all, who gets to decide what is correct? What is considered a disease that needs to be corrected versus a trait that has value in our society? Often here the link is made with the American Eugenics movement and how the ethical implications of some current genomic technologies might relate to the past. PGED has two lessons on eugenics for those interested in learning more.

Slide 4

While the scenario we just discussed is not present-day reality, we do have the ability to edit our DNA. Please watch this clip from the documentary 'The Gene: An Intimate History', to learn more about the discovery of the genome editing technique called CRISPR.

Slide 5



As we saw from the video clip, CRISPR is a genome editing technique that was originally discovered in bacteria. CRISPR can target very specific sections of DNA and make a precise cut at the target size.

Genome editing techniques can be used to do one of two things. First, they can be used to make a gene nonfunctional - for example, to shut down a gene that is causing disease. Alternatively, these techniques can be used to replace one version of a gene with another - for example, to replace a faulty or broken copy of a gene with a functional copy.

So what are the potential applications of CRISPR to human health?

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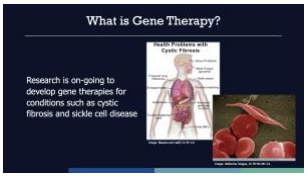

Using genetic technologies such as CRISPR to directly treat the genetic causes of diseases is known as "gene therapy". Because both sickle cell anemia and cystic fibrosis are caused by a change to the DNA in a single gene, they are among the first diseases researchers are trying to address using this approach. The hope is that replacing or correcting the disease-causing gene can perhaps be a cure, or at least prevent the disease from worsening.

A crucial difference between these diseases is where the gene therapy can be administered. Sickle cell anemia affects blood cells, which are produced in the bone marrow. Doctors are able to remove bone marrow from a patient and take it to the lab to perform the gene therapy in a very controlled environment. They can then test the bone marrow cells to make sure the therapy was effective before returning it to the patient. Cystic fibrosis, on the other hand, is more challenging to treat, as it affects multiple organ systems. This means that the gene therapy will have to be introduced into the patient's body, find its way to where it is needed, and make changes to the patient's DNA in a way that is a lot less controlled than treating blood cells in a lab.

Genetic diseases caused by changes in a single gene are prime candidates for gene therapy. However, this is a lot more difficult for more complex conditions, such as heart disease, diabetes and many forms of cancer, as they result from the interplay among many genes as well as between these genes and the environment.

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Scientists are studying how to use CRISPR to treat diseases in animal models, as an important step in the research process towards applications in humans. For example, CRISPR has successfully been used in adult mice to reverse a liver disease called type I tyrosinemia. This disease, which affects 1 in 100,000 people, is caused by mutations in a single gene called FAH. The livers of people with this disease are unable to break down a specific amino acid, which can lead to liver failure.

Scientists injected the CRISPR system, along with working copies of the FAH gene, into the veins of mice with this liver disease. In less than 1% of liver cells in these mice, the faulty FAH gene was successfully replaced with working copies. These edited cells then multiplied and replaced the cells with the faulty FAH gene, and eventually accounted for about 1/3 of liver cells in these animals. This was enough to restore the lost function to the liver, allowing the liver to break down the amino acid it previously could not. This led the research team to declare that they had "cured" type I tyrosinemia in adult mammals. The concept that replacing a piece of DNA could lead to a profound improvement of a serious and often fatal genetic disorder in a mammal brings hope to many.

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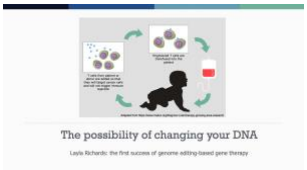

The case of Layla Richards symbolizes the potential promise of genome engineering for treating diseases. Diagnosed at just 14 weeks old with leukemia, a type of cancer that affects blood and bone marrow, Layla Richards was 11 months old when all conventional treatments had failed. Layla became the first child to be treated for leukemia via donated immune cells that were genetically engineered specifically for her body and type of cancer - a kind of treatment called

immunotherapy. The cells, called CAR-T cells, were engineered to attack Layla's cancer cells. The cells were also altered to ensure Layla's immune system would not perceive them as dangerous and reject them. The transplant was a success, and as of the most recent report in early 2017, Layla remained cancer-free.

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So far, we have looked at examples where genome editing was used to directly treat genetic diseases in humans. Now, we are going to look at other applications of genome editing for the benefit of human health.

Here, we ask the question: Might genome editing one day lead to a solution to the global shortage of organs?

There are currently more than 112,000 people on the organ transplant waiting list in the US. Twenty people on that list die each day waiting for an organ. Some researchers think that pigs may offer a solution to this organ shortage, as many pig organs and human organs are similar in size and structure. However, serious challenges persist for potential recipients due to risks of immune rejection and viral infection. Scientists are using CRISPR to alter pig genomes in an effort to address these issues so that people may be more likely to respond well to a transplanted organ from a pig. Increased availability of organs for transplantation could potentially save thousands of lives annually.

This approach raises a number of social and ethical concerns. Animal rights activists worry about the harming and exploitation of animals. The choice of animals in which the organs are produced may present cultural or religious challenges for certain communities. There are also questions

about whether the organs will be available to patients in a fair and equitable fashion. Others worry about the first group of people who agree to such a transplant – will human bodies accept these organs, long term? Will the organs actually function for a length of time that justifies the risks and expense?

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Genome editing is also being considered as an approach to reducing malaria infections.

Each year, hundreds of millions of people get sick from diseases that are spread by mosquitoes, and outbreaks of zika, dengue fever, and yellow fever since the early 2010s highlight the problem. One of the mosquito-borne diseases that leads to the most suffering worldwide is malaria. In 2015, more than 200 million people had the disease, and more than 400,000 people died from it.

Some scientists are investigating the possibility of curbing these mosquito-borne diseases by genetically modifying the mosquitoes, such that they become less able to either reproduce or to carry the disease-causing microbes. The general idea is to release modified mosquitoes into the environment so that they will mate with the wild mosquitoes, and pass the desired trait on to their offspring.

Modifying mosquitoes to change their reproductive ability and population size may have potentially unpredictable ecosystem-wide effects, for example on other animals that may rely on the mosquitoes for food, or plants that may depend on the insects for pollination. In order to balance the potential public health benefits with the ecological effects of this intervention, researchers, policymakers and other

stakeholders are calling for more research before any genetically modified mosquito is widely released into the environment. Our lesson plan Engineering the World Around Us: Genome Editing and the Environment discusses this case in more detail.

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In 2013 it was shown for the first time that CRISPR can be used to edit DNA in human cells. Since then, CRISPR research has moved at a rapid pace.

Only two years later, in 2015, a research group used CRISPR to make genetic changes in non-viable human embryos. And then in 2017, CRISPR was used to make genetic changes in viable human embryos, though these embryos were not allowed to develop past 14 days.

Genetic changes made to the majority of cells in our body - such as our blood cells, lung cells, and liver cells - are not passed onto future generations. However, a genetic change made to germline cells - such as egg and sperm - as well as an early-stage embryo, will be inherited in the genomes of the next generations. This has led to discussion and debate worldwide about whether germline editing in humans is appropriate, and whether or how society should proceed with such research and possible application.

Critics emphasize the technical and ethical issues with making changes to the genome that can be passed down to offspring. There are concerns that any unforeseen effect in the editing process can become inherited. Other questions that are asked include:

- Do we have the right to alter the genome of our future generations?
- Would the editing of certain diseases or disabilities lead to stigmatization of people who are living with those diseases or disabilities? And who gets to decide what are considered diseases or disabilities that should be edited?
- Are there perhaps religious questions and perspectives that can inform the discussion?

At the same time, proponents of germline editing emphasize the benefits in terms of alleviating suffering. These include the potential to eliminate diseases such as Huntington's disease, a debilitating neurological condition caused by a single gene variant. They also argue that humans have long been altering the lives and genetics of our offspring without their explicit consent, through procedures such as genetic counseling and preimplantation genetic diagnosis.

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So, what is the path forward?

A number of meetings and working groups have occurred over the years to move the conversations forward. Meetings including the International Summit on Human Gene Editing, which convened scientists, social scientists, ethicists, and other stakeholders in December 2015. A statement released at the end of this summit emphasized that it would be "irresponsible" at this time to proceed with the clinical use of germline editing, but it did not recommend banning the technique, instead suggesting that research should continue.

In February 2017, an expert panel convened by the US National Academies issued its report on human genome editing. It recommended that clinical research on germline modification to treat "serious disease or condition" should be allowed to proceed once a number of criteria are met, including more research on safety and efficacy, stringent oversight, and continuing public conversation about societal benefits and risks. The report urges that genome editing for nonmedical "enhancement" should not proceed without further societal discussion.

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Despite the international moratorium, or 'pause', on germline editing, a researcher named Dr. He announced in late 2018 that two children had been born whose genes were edited in the embryo stage. In an attempt to give immunity to HIV infection, he genetically modified the CCR5 gene in embryos via in-vitro fertilization. This is the first report of human beings being born with their DNA purposely altered in a lab to possess certain traits.

In addition to the issues that this case raised about informed consent and the ethics of germline modification in humans, there are also scientific questions to consider regarding the effectiveness of the edits and potential unintended consequences.

PGED has a full lesson on this story if you are interested in learning more.

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In this presentation, we have discussed the rapidly evolving field of genome editing and looked in more detail at one of its newest technologies - CRISPR. While genome editing offers a potential solution to many human health issues, including genetic and insect-borne diseases, certain forms of cancer, and the shortage of human transplant organs, it brings just as many ethical questions. The challenge before us is to find a way to realize the potential benefits of this technology while minimizing the risks and making sure its implementation is ethical and equitable.