Genome Editing and Engineering
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Module - 12
Ethical concerns: Germ line gene editing
Lecture - 48
Bioethics and Biosafety - Part B

Welcome to the course on Genome Editing and Engineering. We are discussing about ethical concerns in germ line editing and the module number 12. In part B of this lecture on Bioethics and Biosafety, we will continue the discussion which was started in part A.

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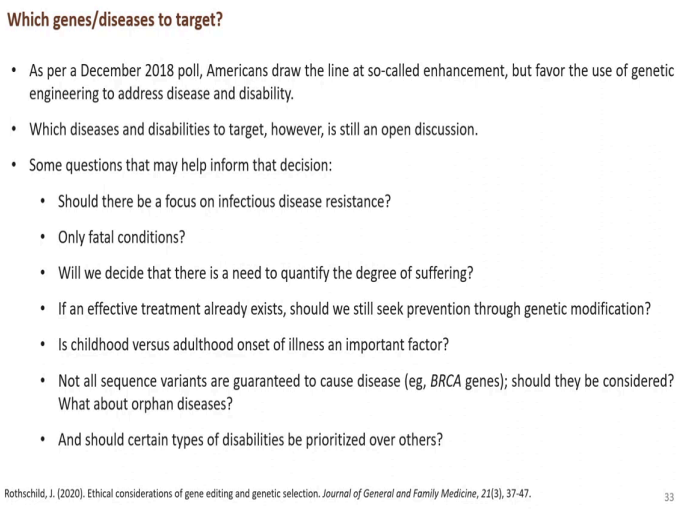

So, when it comes to germline editing or genome editing application in human diseases, which genes and diseases to target is an important question. As per a poll in December 2018, US citizens draw the line at the so-called enhancement, but favour the use of genetic engineering to address diseases and disability.

And which type of disease and disabilities need to be targeted, however, is still an open discussion. Some of the questions that may help inform that decisions are: should there be a focus on infectious disease resistance? Or whether only fatal conditions are to be considered? Will we decide that there is a need to quantify the degree of sufferings? If an effective

treatment already exists should we still seek prevention through genetic modification? If salute versus adulthood onset of illness is an important factor?

Not all sequence variants are guaranteed to cause disease; should they be considered? What about orphan diseases and should certain types of disabilities be prioritized over others? These are very important questions which have been discussed by Rothschild in this article published in 2020 called Ethical considerations of gene editing and genetic selection, published in Journal of General Family Medicine.

For more details, for those who are interested kindly refer to these particular journal article, from which we have drawn these important points raised by these opinion poll.

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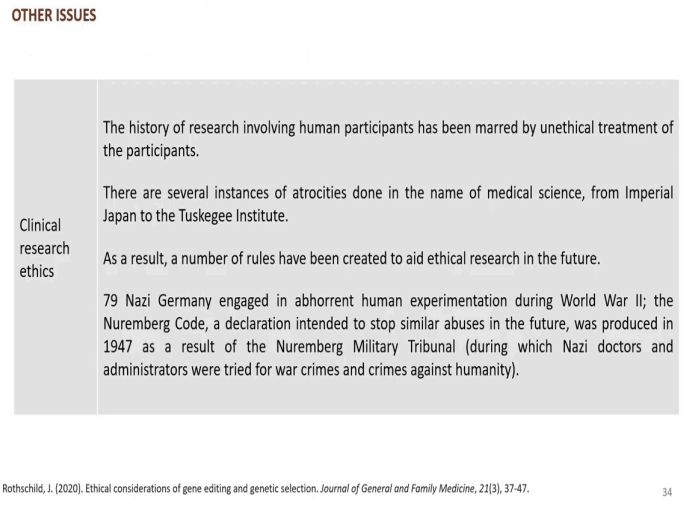

There are certain other important issues in association with this. For example, in clinical research ethics the history of research involving human participants has been made by unethical treatment of the participants. There are several instances of atrocities done in the name of medical science from imperial Japan to the Tuskegee Institute.

And we have already discussed about the atrocities in the Nazi Germany and the Nuremberg trial and as a result a number of rules have been created to aid ethical research in the future. So, we have already discussed at length about the Nuremberg trial and we will not discuss these again due to positive of time.

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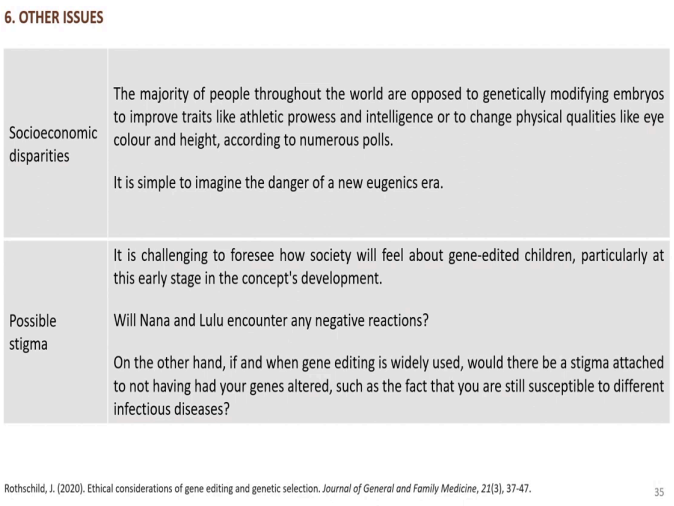

Then other things are the socioeconomic disparities the majority of people throughout the world are opposed to genetically modifying embryos to improve traits like athletic powers and intelligence or to change physical qualities like eye colour and height according to numerous poles. So, people are thinking about designer babies, in these era of gene editing. So, these are very very important ethical issues and they take us to an era or dangerous era of a new eugenics era which has to be avoided.

And there are certain possible static stigma which can be associated, it is challenging to foresee how society will feel about gene edited children particularly at these early stage in the concepts development. Will Nana and Lulu encounter any negative reactions. So, these are the children which were created by genome edited zygotes by He Jiankui, we will decide discuss about them in one of the slides later and also He Jiankui.

On the other hand if and when gene editing is widely used, would there be a stigma attached to not having had once genes altered such as the fact that you are still susceptible to different infectious these days.

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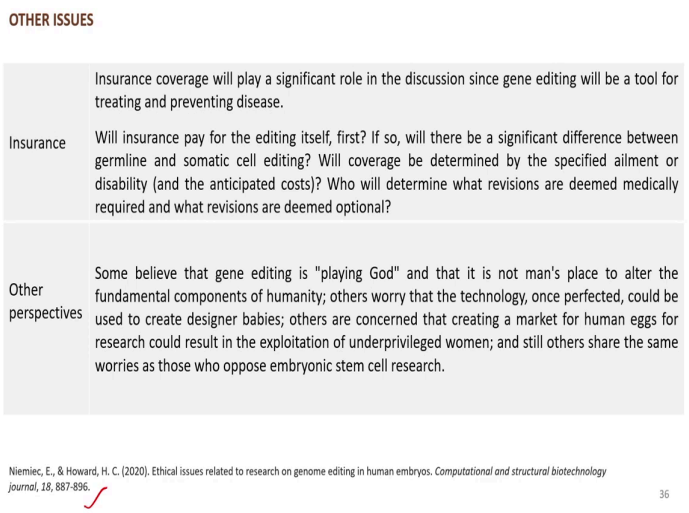

Their concerns regarding insurance, medical insurance or life insurance because the insurance coverage will play a significant role in the discussions since gene editing will be a tool for treating and preventing diseases. Will the companies pay for the editing itself first? If so will there be a significant difference between germline and somatic cell editing? Will coverage be determined by the specified ailment or disability? Who will determine what revisions are deemed medically required and what revisions are deemed optional?

And other perspectives like some believe that gene editing is “playing god” and it is not man’s place to alter the fundamental components of humanity. Others worry that the technology, once perfected, could be used to create designer babies; others are concerned that creating a market for human eggs for research could result in the exploitation of underprivileged women. And still others shared the same worries as those who oppose embryonic stem cell research.

So, these important issues have been adopted from the article by Niemiec E and Howard H. C in the Ethical issues related to a research and genome editing in human embryos, published in Computational and Structural Biotechnology Journal published in 2020 those who are interested for further details can consult these particular article.

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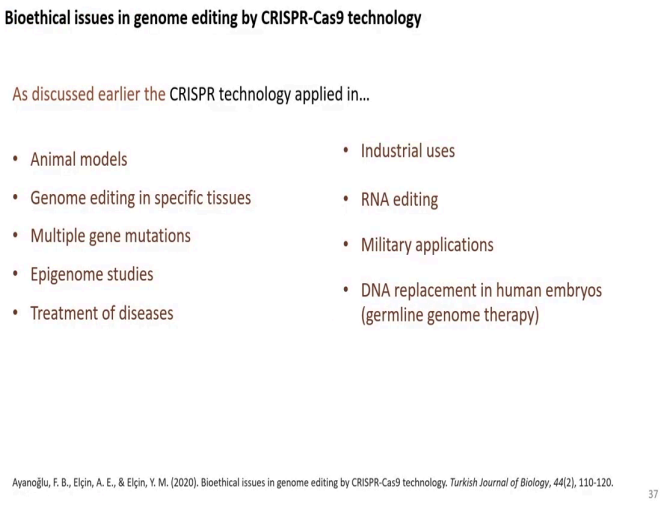

Let us now discuss in particular the bioethical issues in genome editing by CRISPR-Cas9 technology leaving aside ZFN and TALEN. So, with CRISPR-Cas9 technology we can develop animal models, then we can go for genomic editing, specific tissues in genes, multiple genetic mutations can be done. There can be epi genome studies and treatment of diseases, it is also useful in industry then possibility of RNA editing, military applications DNA replacement in human embryos the germline genome therapy.

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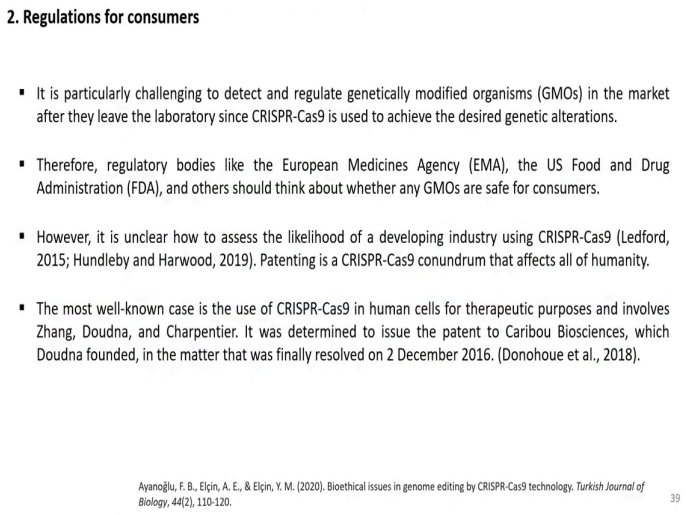

Regulations for the consumers: it is particularly challenging to detect and regulate genetically modified organisms in the market after they leave the laboratory since CRISPR-Cas9 is used to achieve the desired genetic alterations and it do not have any markers associated with it. Therefore, regulatory bodies like the European Medicines agency, the US Food and Drug administration and others should worry about whether any genome are safe for consumers.

But it is unclear how to assess the likelihood of a developing industry using CRISPR-Cas9; patenting is a CRISPR-Cas9 conundrum it affects all of humanity. The most well-known case is the use of CRISPR-Cas9 in human cells for therapeutic purposes and it involved Zhang, Doudna, and Charpentier. It was determined to issue a patent to Caribou Biosciences, which Doudna found it in the matter that was finally resolved on 2nd December 2016.

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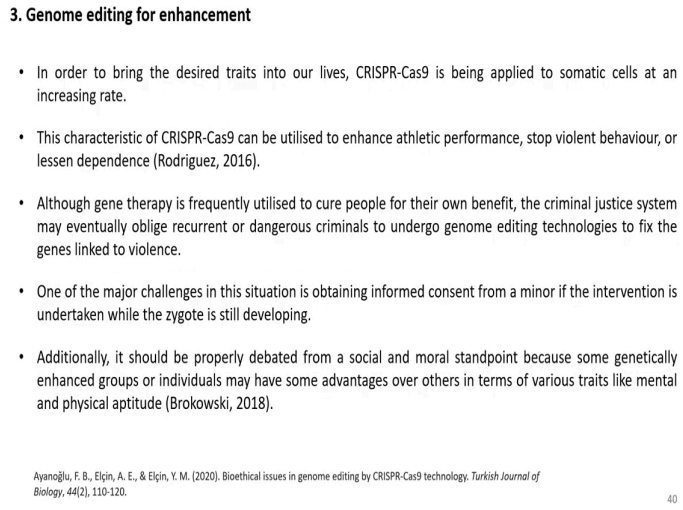

Genome editing for enhancement in order to bring the desired trait into our lives, CRISPR-Cas9 is being to applied somatic cells at an increasing rate. These characteristics of CRISPR-Cas9 can be utilised to enhance athletic performance stop violent behaviour, or lessen dependence as visualized by various scientists. Although gene therapy is frequently utilized to cure people for their own benefit, criminal justice system may eventually oblige recurrent or dangerous criminals to undergo genome editing technologies to fix the genes linked to violence these are some of the futuristic scenarios.

One of the major challenges in this situation is obtaining informed consent from a minor, if the intervention is undertaken while the zygote is still developing. Additionally, it should be

properly debated from a social and moral standpoint, because some genetically enhanced groups or individuals may have some advantages of others in terms of various traits like mental and physical aptitude.

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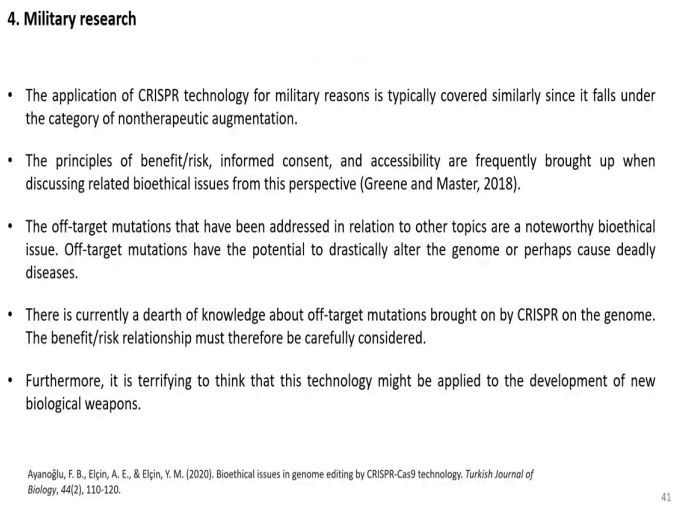

In military research the application of CRISPR technology in defence research or purposes is typically covered similarly, since it falls under the category of non therapeutic augmentation. The principles of benefit risk inform constant and accessibility are frequently brought up when discussing related bioethical issues from these perspectives.

The emergence of in CRISPR army is also raising concerns in the scientific community and the off-target mutations that have been addressed in relation to other topics are a noteworthy bioethical issue. Off-target mutations have the potential to drastically alter the genome or perhaps cause deadly diseases. There is currently a dearth of knowledge about off target mutations brought on by CRISPR on the genome, the benefit or risk relationship must therefore be carefully considered.

Furthermore, it is terrifying to think that this technology might be applied to the development of new biological weapons.

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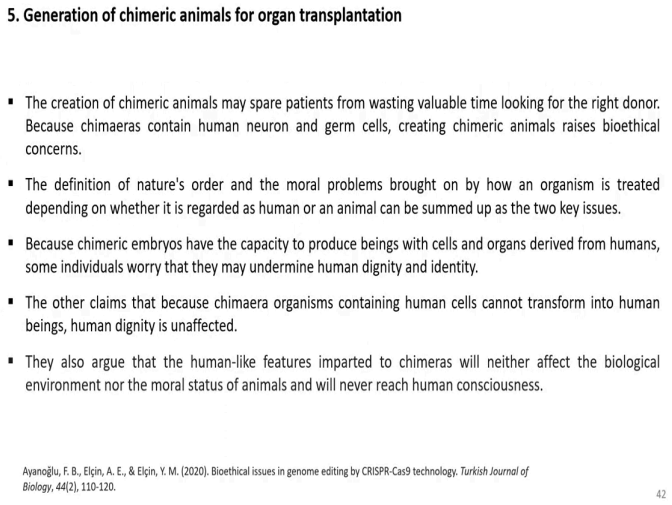

Generations of chimeric animals for organ transplantation. The creation of chimeric animals may pay patients from wasting valuable time looking for the right donor. Because chimeras contain human neuron and germ cells creating chimeric animals resist bioethical concerns. We have discussed about the humanization of animals especially pigs for organ development in one of our earlier classes.

The definition of natures order and the moral problems brought on by how an organism is treated depending on whether it is regarded as human or an animal can be summed up as the two key issues. Because chimeric embryos have the capacity to produce individuals with cells and organs derived from humans. Some individuals worry that they may undermine human dignity and identity.

The other claims that because chimera or organisms contain human cells, cannot transform into human beings human dignity is unaffected. So, certain chimera animals with human cells as pointed in point number 3 are going to raise concerns. Because as it is part human, whether the human dignity and identity is some kind of under undermined from the point of view of ethics.

They also argue that the human like features imparted to chimeras will neither affect the biological environment nor the moral stress of animals and will never reach human consciousness.

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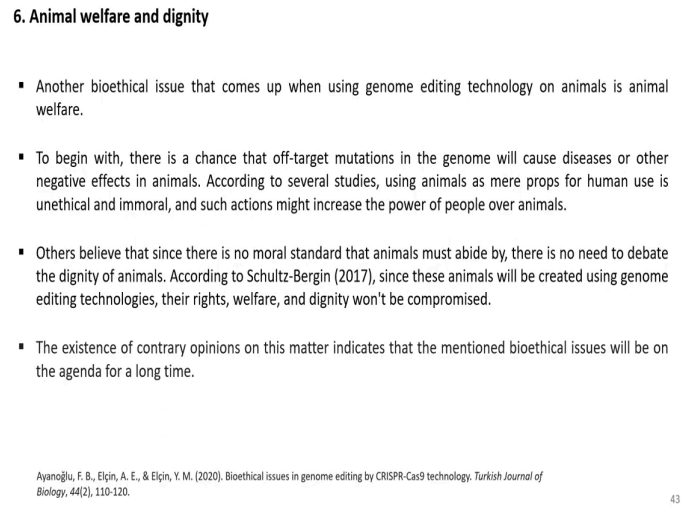

The next important issue is the animal welfare and dignity: that comes up when using genome editing technology on animals. And to begin with there is a chance that off target mutations in the genome will cause diseases or other negative effects in animals. According to several studies using animals as mere props for human use is unethical and immoral.

And just actions might increase the power of people over animals. Others believe that since there is no moral standard that animals must abide by, there is no need to debate the dignity of animals. According to Schultz-Bergin, since these animals will be created using genome editing technology their rights welfare and dignity will not be compromised; however, a majority of people do not agree to these kind of notions.

The existence of contrary opinions on the matter indicates that the mentioned bioethical issues will be on the discussion and as in the for a long time in future.

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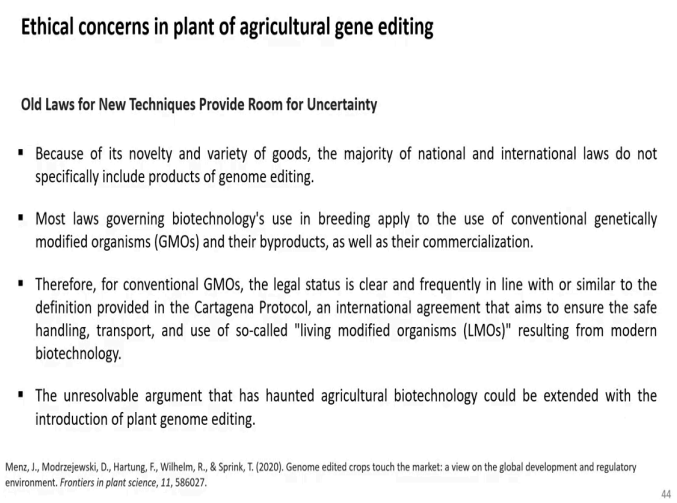

The ethical concerns in plant of agricultural gene editing. The old laws for new techniques provide room for uncertainty, due to novelty and variety of goods the majority of national and international laws do not specifically include products of genome editing. Most laws governing biotechnologies use in breeding apply to the use of conventional genetically modified organisms and their by-products as well as their commercialization.

Therefore, for conventional GMOs the legal status is clear and frequently in line or sync with the similar definition provided for the Cartagena protocol. An international agreement that aims to ensure the safe, handling, transport and use of so called “living modified organisms” resulting from modern biotechnology. The unresolvable argument that has haunted agricultural biotechnology could be extended with the introduction of plant genome editing.

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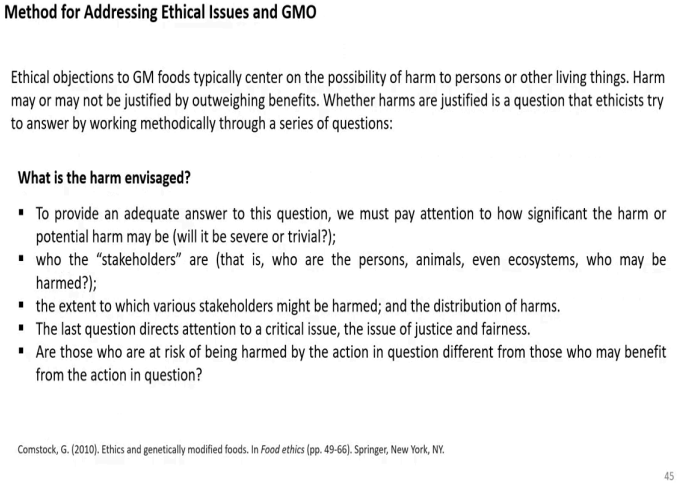

Methods were addressing ethical issues and GMOs ethical objections to genetically modified foods typically centre on the possibility of harm to persons or other living things. Harm may or may not be justified by outweighing the benefits, whether harms are justified is a question that ethicists try to answer by working methodically through a series of questions.

And in this regard, it is often asked what is the harm emphasis? To provide an adequate answer to this question we must pay attention to how significant the harm or potential harm may be. Who the stakeholders are? That is who are the persons, animals, even ecosystems who may be harmed?

The extent to which various stakeholders might be harmed and the distribution of the harms. The last question directs attention to a critical issue, the issue of justice and fairness. Are those who are at risk of being harmed by the action in question different from those who may benefit from the action in question?

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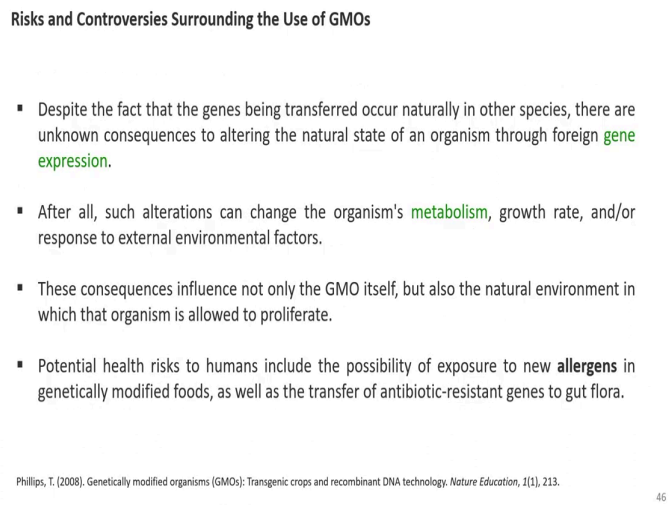

What are the risks and controversy surrounding the use of GMOs? Despite the fact that the genes being transferred occur naturally in other species, there are unknown sequences to altering the national state organism through a forensic expression using recombine in DNA technology. After all such alterations can change the organism's metabolism, growth rate and our response to external environmental factors.

These consequences influence not only the GMO itself, but also the natural environment in which the organism is allowed to proliferate. Potential hell tricks to humans include the possibility of exposure to new allergens in genetically modified foods, as well as the transfer of antibiotic resistance genes to gut flora.

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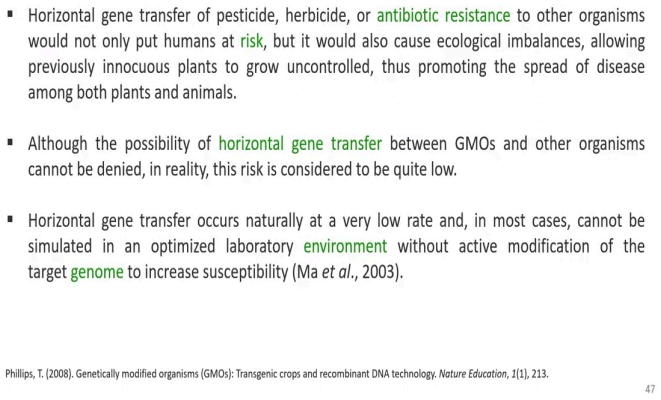

Horizontal gene transfer of pesticide, herbicide, or antibiotic resistance genes to other organisms would not only put humans at risk, but it would also cause ecological imbalances allowing previously innocuous plants to grow uncontrol. Thus, promoting the spread of disease among both plants and animals.

Although the possibility of horizontal gene transfer between GMOs and other organisms cannot be denied, in reality this risk is considered to be quite low. Horizontal gene transfer occurs naturally at a very low rate and in most cases, cannot be simulated in an optimized laboratory environment, without active modification of the target genome to increase susceptibility, as reported by Ma *et al.,* 2003.

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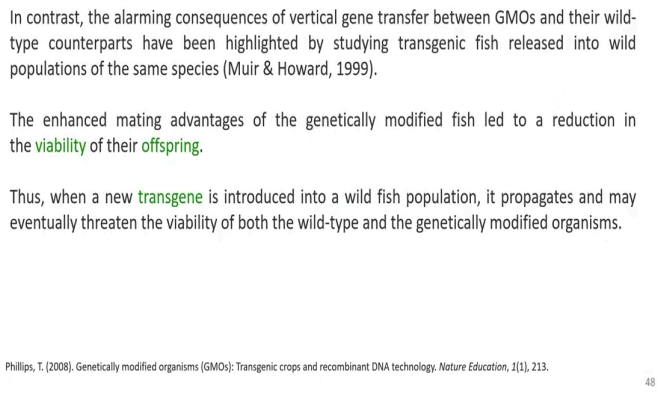

In contrast, the alarming consequences of vertical gene transfer between GMOs and their wild type counterparts have been highlighted by studying transgenic fish released into wild populations of the same species. The enhanced making advantage of the genetically modified fish led to a reduction in the viability of the offspring.

Thus, when a new transgene is introduced into a wild fish population it propagates and may eventually threaten the viability of both the wild type and the genetically modified organisms.

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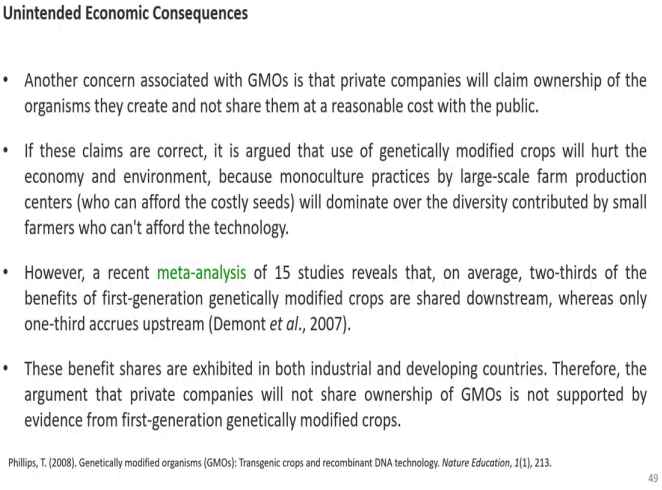

Some of the unintended economic consequences are also there. For example, there is a concern associated with GMOs, GMOs that private companies will claim ownership of the organisms, they create and not share them at a reasonable cost with the public. If these claims are correct, it is argued that use of genetically modified crops will hurt the economy and environment, because monoculture practices by large scale farm production centres will dominate over the diversity controlled by small farmers who cannot afford the technology.

Our recent meta-analysis of 15 studies reveals that on average two-thirds of the benefits of first generation genetically modified crops are shared downstream, whereas, only one third accrues upstream. These benefit shares are exhibited in both industrial and developing countries. Therefore, the argument that private companies will not share ownership of GMO is not supported by evidence from first generation genetically modified crops.

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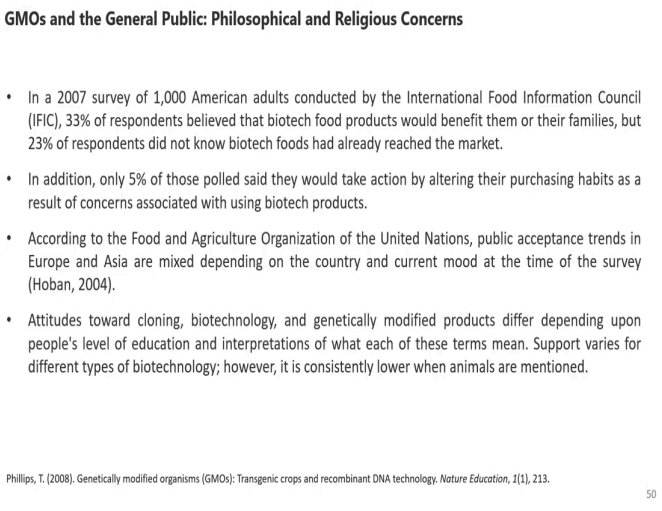

GMOs and the general public philosophy and religious concerns. In 2007, a survey of 1000 American adults conducted by the International Food Information Council had some interesting facts. 33 percent of respondents believe that biotech food products would benefit them or their families, but 23 percent of respondents did not know biotech foods has already reached the market.

Only 5 percent of those polled said that they would take action by altering their processing habits as a result of concerns associated with using biotech products. According to the Food

and Agriculture Organization of the United Nations public, acceptance trends in Europe and Asia are mixed depending on the country and current mood at the time of the survey.

Attitudes towards cloning biotechnology and genetically modified products differ, depending upon people's level of education and interpretations of what each of these terms means, support varies for different types of biotechnology. However, it is consistently low when animals are mentioned.

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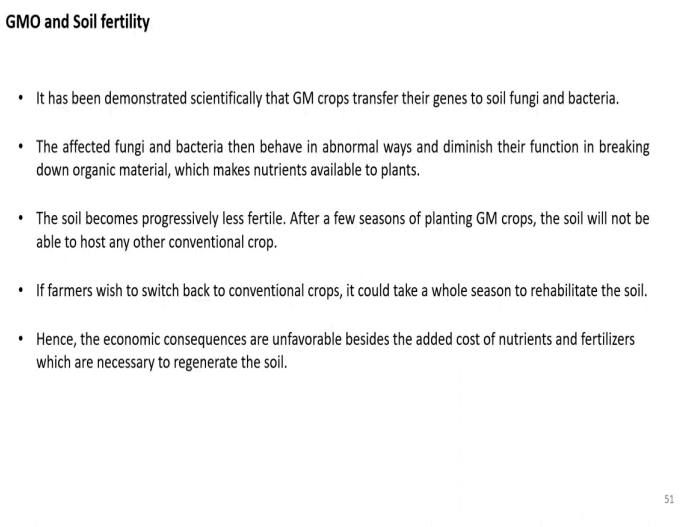

GMO and soil fertility is also one important aspect, it has been demonstrated scientifically that genetically modified crops transfer, the genes to soil fungi and bacteria. The affected fungi and bacteria behave in abnormal ways and diminish their function in breaking down organic materials which make nutrients available to plants.

Soil becomes progressively less fertile. After a few seasons of planting GM crops the soil will not be able to host any other conventional crop. If farmers wished to switch back to conventional crops, it would take a whole season to rehabilitate the soil. Hence the economic consequences are unfavourable, besides the added cost of nutrients and fertilizers which are necessary to regenerate the soil are also important issues.

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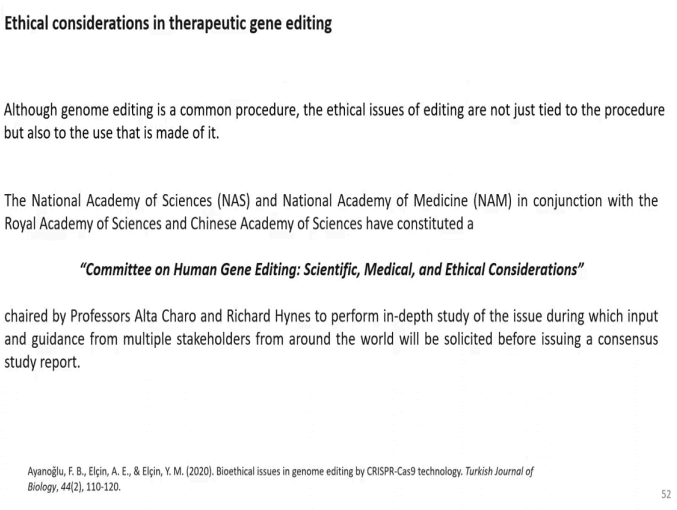

Ethical concerns in therapeutic gene editing. Gene editing is have become a common procedure as you can understand from the many discussions we had in this particular course, starting from mega nucleases to CRISPR-Cas9. How about the ethical issues of editing and not just type to the procedures, but also to the use that is made of it.

The National Academy of Sciences and the National Academy of Medicine, in conjunction with the Royal Academy of Sciences and Chinese Academy of Sciences have constituted a committee on human gene editing, scientific medical and ethical considerations shared by Professors Alta Charo and Richard Hynes to perform in depth study on the issues during which input and guidance from multiple stakeholders from around the world will be solicited before is seeing a consensus study report.

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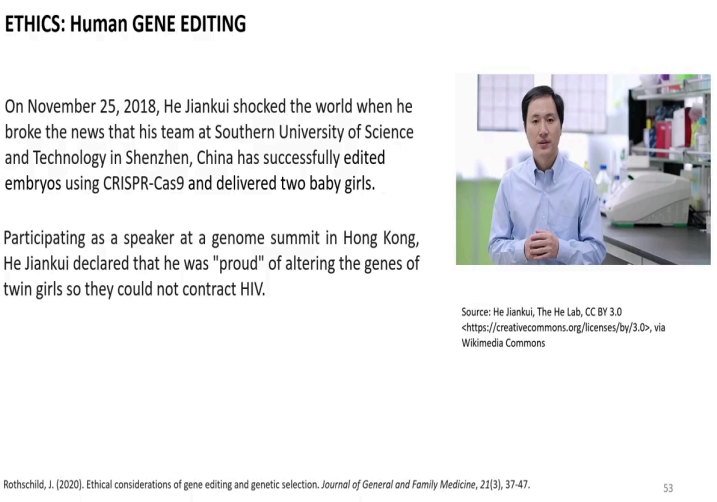

This is one of the blatant misuse of the technology on November 25 2018, He Jiankui shocked the world when he broke the news that his team at Southern University of Science and Technology in Shenzhen, China had successfully edited embryos using CRISPR-Cas9 technology and have successfully delivered to baby girls who will be resistant to HIV.

We have discussed about the HIV resistance in the Scandinavian population due to the CCR 5 delta 32 mutation. He Jiankui and his team edited these zygotes to create the mutation, which will make them resistance to HIV. He participated as a speaker at a genome summit in Hong Kong and he declared with immense pride of altering the genes of the tween girls. So, they could not contract HIV in future. Later on, it was found a third child was also delivered.

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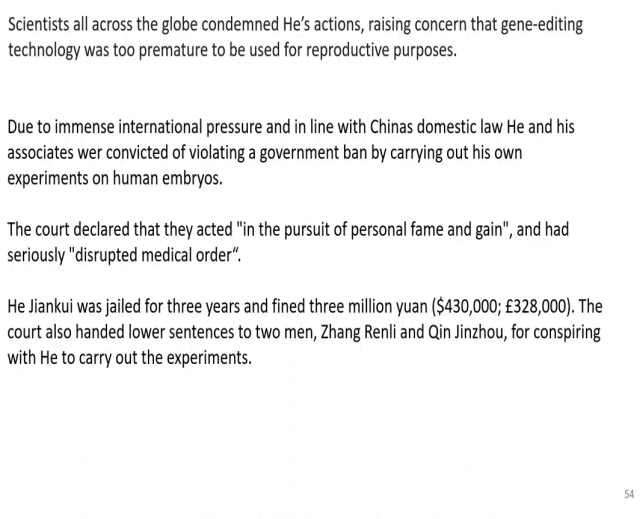

Scientists all across the globe condemned He Jiankui and He's teams action, and raised concern and alarmed that gene editing technology was too premature to be used for reproductive purposes. And due to immense international pressure and in line with the Chinese Domestic Law, he and his associates were convicted of violating a government ban by carrying out his own experiments on human embryos.

The court declared that he and his team has acted "in the pursuit of personal fame and gain" and had seriously "disrupted medical order". He Jiankui was jailed for 3 years and fined 3 million yuan. The court also handed lower sentences to two other men Zhang Renli and Qin Jinzhou for conspiring with He to carry out the experiments.

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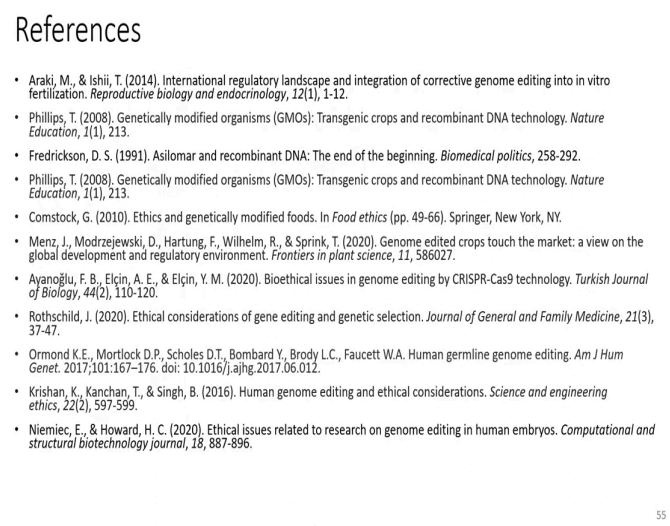

So, with this we come to an end on the discussion of bioethics and biosafety. These are some of the articles we have consulted for preparing this particular lecture. For any details on any of the concepts that we have put forward in this discussion you may refer to these articles.

Thank you for your patient hearing.