Genome Editing and Engineering
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Module - 12
Ethical concerns: Germ line gene editing
Lecture - 47
Bioethics and Biosafety - Part A

Welcome to my course on Genome Editing and Engineering. In this module we are going to discuss about Ethical concerns with respect to Germ line gene editing. We will begin with some discussion in Bioethics and Biosafety let us now first look into the origins of the term bioethics.

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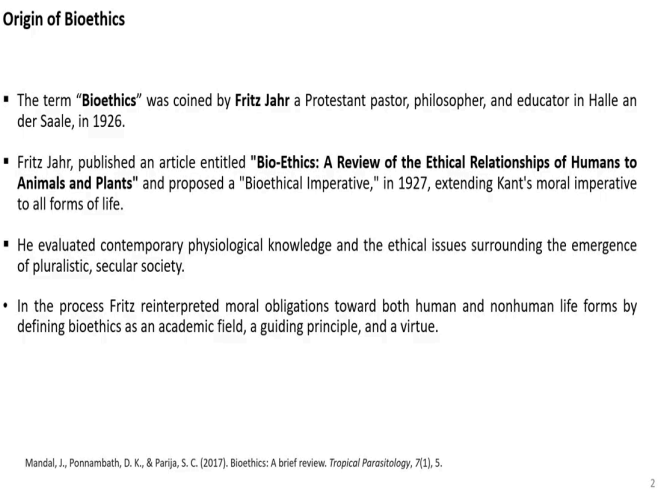

The term bioethics was coined by Fritz-Jahr a Protestant pastor, philosopher, and educator in Halle an der Saale in 1926.

Fritz published an article entitled Bio-Ethics: A Review of the Ethical Relationship of Humans to Animals and Plants and proposed a “Bioethical Imperative” in 1927, extending Kant’s moral imperative to all forms of life. He evaluated contemporary physiological knowledge and the ethical issues surrounding the emergence of pluralistic secular society. In the process Fritz reinterpreted moral obligations toward both human and non human life

forms by defining bioethics as an academic field a guiding principle and a virtue. Let us look into some historical developments in the field.

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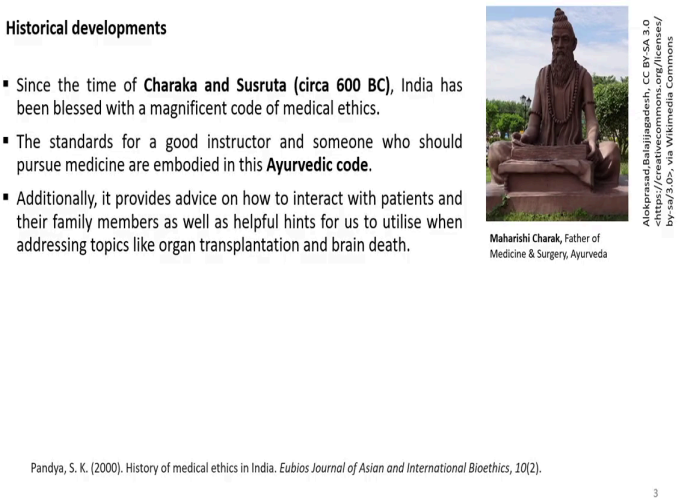

Since, the time of Charaka and Susruta India has been blessed with a magnificent code of medical ethics. The standards for a good instructor and someone who should pursue medicine are embodied in the code of Ayurveda. Additionally, Ayurveda provides advice on how to interact with patients and their family members as well as helpful hints for us to utilize when addressing topics like organ transplantation and a brain death in the current context.

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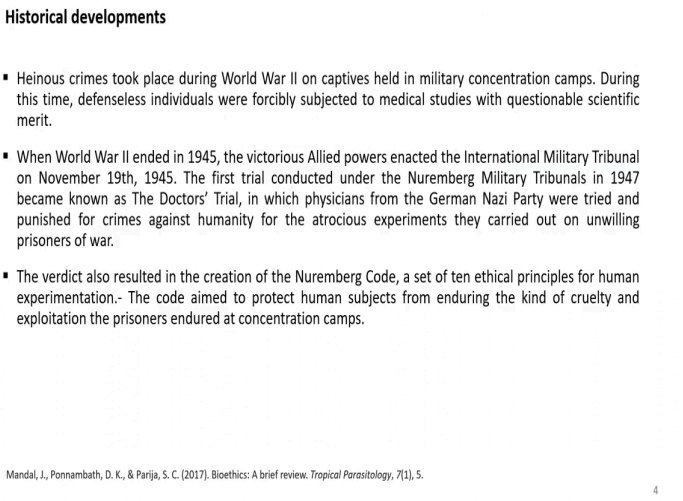

If you go back to the era of World War II a heinous crimes took place on captives held in military concentration camps in Nazi Germany during this time defenceless individuals were forcibly subjected to medical studies with questionable scientific merit. When the war ended in 1945, the victorious Allied powers enacted the International Military Tribunal on November 19th, 1945.

And in one of the first trials conducted under the Nuremberg Military Tribunals in 1947 which became famous as The Doctor's Trial, in which physicians from the German Nazi party were tried and punished for crimes against humanity for the atrocious experiments they carried out on unwilling prisoners of war.

These verdict also resulted in the creation of the Nuremberg Code, a set of ten ethical principles for human experimentation. The code aim to protect human subjects from enduring the kind of cruelty and exploitation the prisoners endured at the concentration camps.

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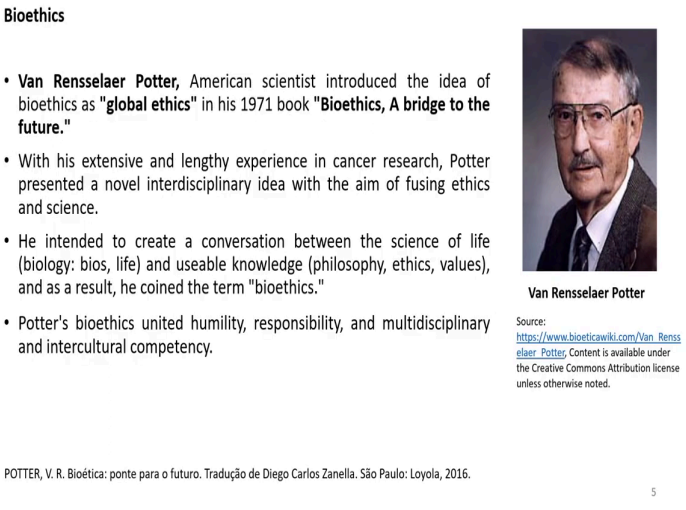

Van Rensselaer Potter an American scientist introduced the idea of bioethics as global ethics. In his 1971 book Bioethics, A bridge to the future." With his extensive and lengthy experience in cancer research, Potter presented a noble interdisciplinary idea with the aim of fusing ethics and science.

He intended to create a conversation between the science of life and usable knowledge and as a result, he coined the term "bioethics". Potter's bioethics united humility, responsibility, and multidisciplinary and intercultural competency.

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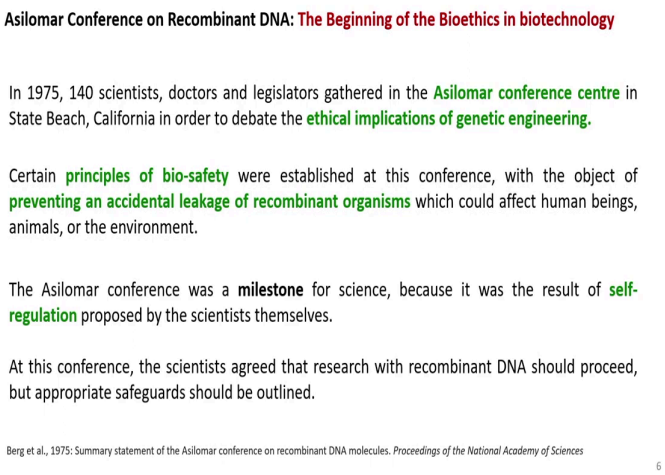

One of the landmark events in the field of bioethics and bio safety is the Asilomar Conference on Recombinant DNA, which is also considered as the Beginning of Bioethics in the field of a biotechnology.

In 1975, about 140 scientists, doctors and legislators gathered in the Asilomar conference centre in State Beach, California in order to debate the ethical implications of a genetic engineering. Certain principles of bio-safety were established at this conference, with the object of preventing an accidental leakage of recombinant organisms which could affect human beings, animals, or the environment.

The Asilomar conference was a milestone for science, because it was a result of self-regulation proposed by the scientists themselves. At this conference, the scientists agreed that research which recombinant DNA should proceed, but appropriate safeguards should be outlined.

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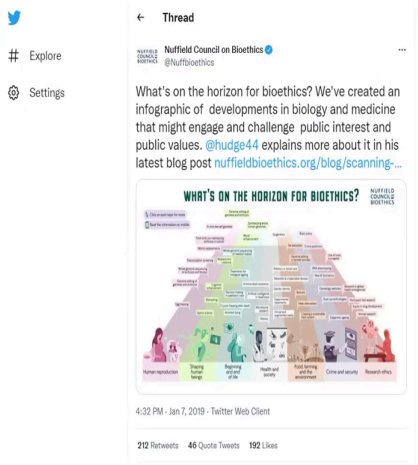

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Since this meeting a lot of developments has happened in the field of bioethics, bio safety and regulation. And now many of these operating principles and guiding principles are applied to the field of a gene editing and also some new guidelines have come up in the recent years to help the field of genome editing grow and prosper in a safer way and in a more human way.

Let me share with you a tweet by Nuffield Council on a Bioethics, you can see here this particular tweet on January 7, 2019 and the Nuffield Council on Bioethics has presented here a beautiful graphics depicting what is on the horizon for bioethics when they have declared to have created a infographic of developments in biology and medicine that might engage and challenge public interest and public values.

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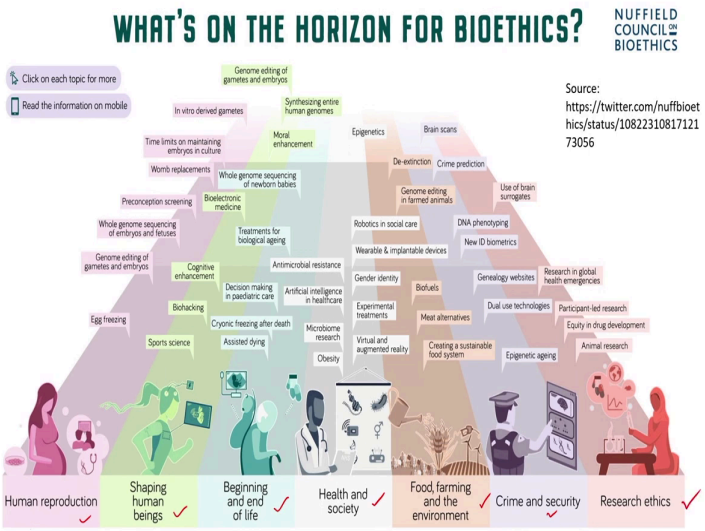

Bioethics ethics is a very big subject as you can see from these graphics by Nuffield Council on Bioethics ranging from human reproduction to saving shaping human beings or the birth and death, health and society food farming and environment even crime and security and finally, impacting research ethics.

So, I will not going to detail of this infographics, but you can see here the Genome editing of gametes and embryos and other important trending topics in the field of modern biology like whole genome sequencing of embryos and fetuses also womb replacements and then synthesizing entire a human genomes.

The idea of showing you these graphics is to show you the contextual relevance of the genome editing in respect to bioethics and how it is becoming one of the a main topic of concern and discussions. So, there are others like treating of biological ageing and or maybe decision making in paediatric care, then microbiome resource many of these include the intervention of either genetic engineering or genome editing and one of the area is the epigenetic adding ageing and also the epigenetics as a whole has a lot of importance from the point of view of bioethics.

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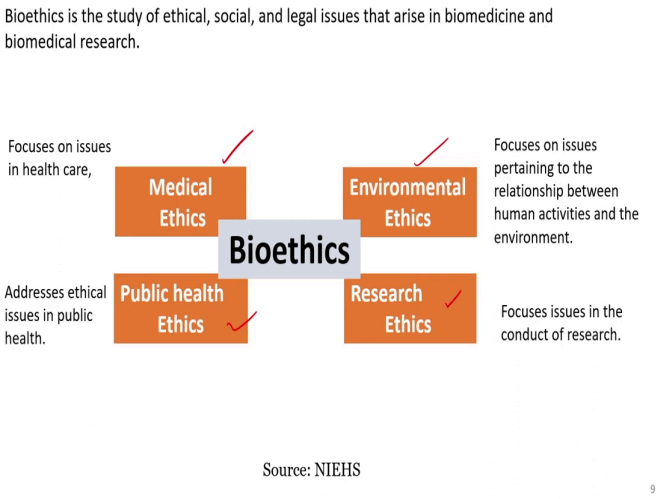

So, let us now try to understand what actually is bioethics. Bioethics is the study of ethical social and legal issues that arise in biomedicine and biomedical research as defined by NIEHS and you can see bioethics is not just one simple thing so many different aspects are connected to bioethics. So, it has many sub domains or sub disciplines like medical ethics, environmental ethics, a public health ethics and research ethics, each of these sub disciplines focuses on different issues.

For example, medical ethics focuses on issues in health care, environmental ethics focuses on issues pertaining to the relationship between human activities in the environment, public health issues addresses ethical issues in public health while research ethics focuses issues in the conduct of research.

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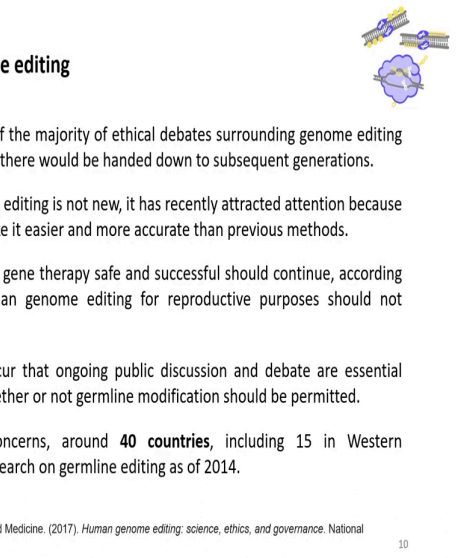

Let us discuss a little bit about the ethical concerns in human gene editing. The human germ line is the focus of the majority of ethical debates surrounding genome editing since any modifications performed there would be handed down to subsequent generations as it is inheritable.

Although the discussion of genome editing is not new, it has recently attracted attention because of the finding that CRISPR may make it easier and more accurate than previous methods like ZFN, TALEN or mega nucleases and studies that would make gene therapy safe and successful should a continue; however, according to bioethicists and experts. Human genome editing for reproductive purposes should not apparently be undertaken as expressed by many bioethicists.

The majority of stakeholders agree that ongoing public discussion and debate are essential to let the public determine whether or not germ line modification should be permitted and due to ethical and security concerns around 40 countries, including 15 in the Western Europe, have prohibited or outlawed research on germline editing back in 2014.

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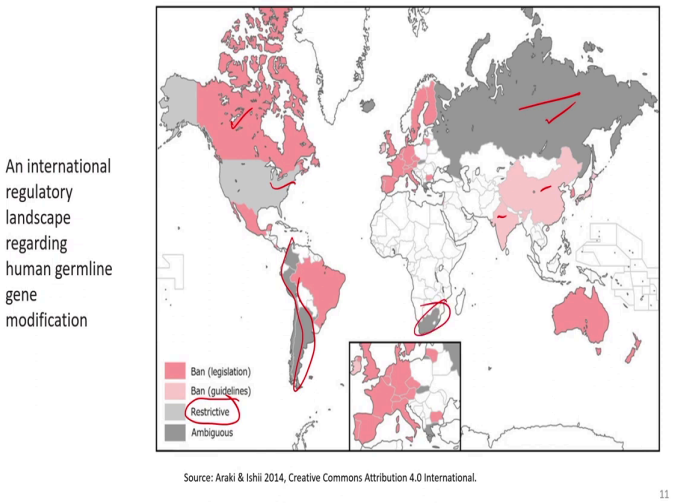

So, this is an international regulatory landscape regarding germ line human germ line gene modification. You can see these countries with the dark color where it is banned through legislation. While countries like India, China there are guidelines issued for ban and then many countries there are total restriction, it is restrictive. How are the countries like here USSR and also some Latin American countries or some countries in Africa where the position is ambiguous.

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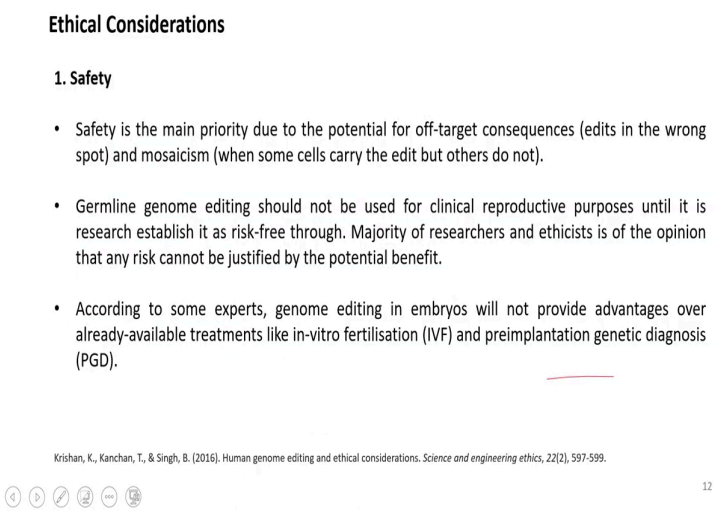

What are their various ethical considerations? The number 1 is safety. It is the main priority due to the potential for off-target consequences or they may be editing in the wrong spot and mosaicism when some cells carry the edit, but others do not. Germline genome editing should not be used for clinical reproductive purposes until it is established through research as a risk-free technique.

Majority of researchers and ethicists of the opinion that any risk cannot be justified by the potential benefit that is going to bring. According to some experts, genome editing in embryos will not provide any advantage over already available treatments like in vitro fertilization and pre-implantation genetic diagnosis. So, it should be discouraged from being used.

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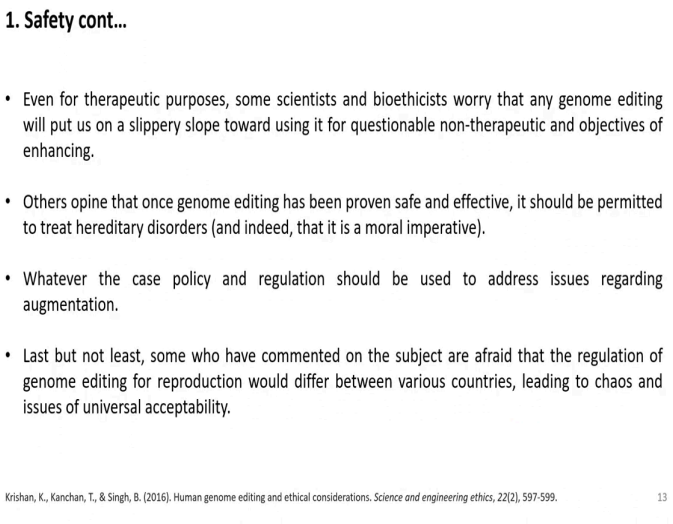

Even for therapeutic purposes, many worry that any genome editing will put us on a slippery slope towards using it for questionable non-therapeutic and objectives of enhancing of particular characters or phenotypes. Others are of the opinion that once genome editing has been proven to be a safe and effective technology, then it should be permitted to treat hereditary disorders as there are many people who are suffering due to genetic diseases.

Whatever the case policy and regulation should be used to address issues regarding augmentation and last, but not the least some who have commented on the subject are afraid that the regulation of genome editing for reproduction would differ between various countries leading to chaos and issues of universal acceptability.

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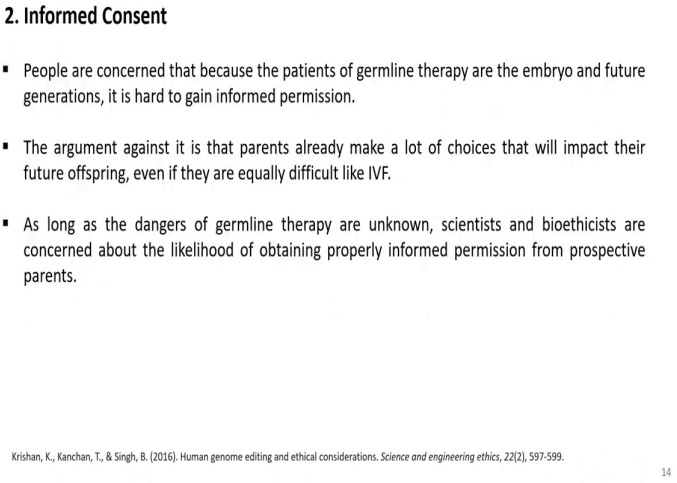

The 2nd most important thing is informed consent people are concerned that because the patients of germline in germline therapy are the embryo and the future generations and yet unborn it is hard to gain informed permission. For this there is an counterargument, that parents already make a lot of choices that will impact their future offsprings even if they are equally difficult like in the case of IVF. As long as the dangers of germline therapy are unknown, scientists and bioethicists are concerned about the likelihood of obtaining properly informed permission from prospective parents.

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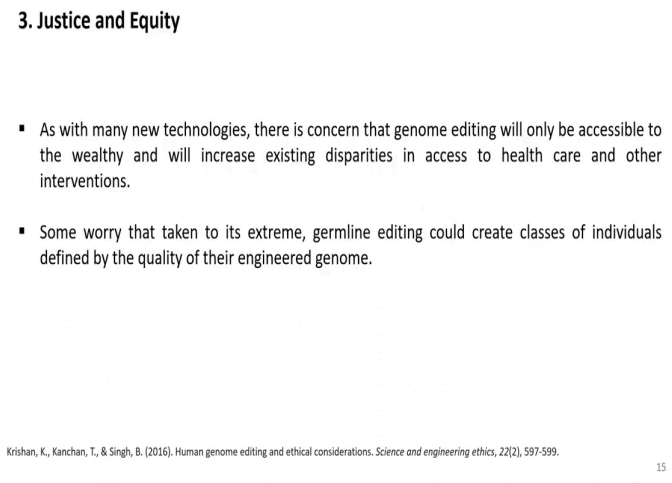

The third important point is justice and equity. As it happens with any emerging new technologies there is a concern that genome editing will only be accessible to do wealthy and will increase existing disparities in access to healthcare and other interventions. Many worry that taken to its extreme; germline editing could create classes of individuals defined by the quality of their engineered genome.

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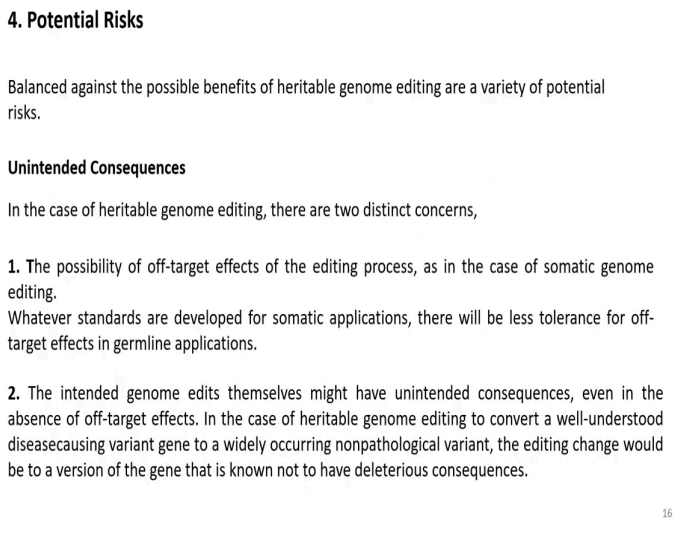

One of the important points is the potential risks due to this technology and there are definitely certain benefits of heritable genome editing but there are also equal the various kinds of potential risk associated with the technology. We are not aware of certain unintended consequences for example, in case of heritable genome editing there are two distinct concerns expressed by the scientific community.

Number 1 is the possibility of off-target effects of the editing process as in the case of somatic genome editing and whatever standards are developed for somatic applications there will be less tolerance for off-target effects in germ line applications. 2nd is the intended genome edits themselves might have unintended consequences even in the absence of off-target effects. In the case of heritable genome editing to convert a well understood disease causing variant gene to a widely occurring non pathological variant, the editing change would be to a version of the gene that is known not to have deleterious consequences.

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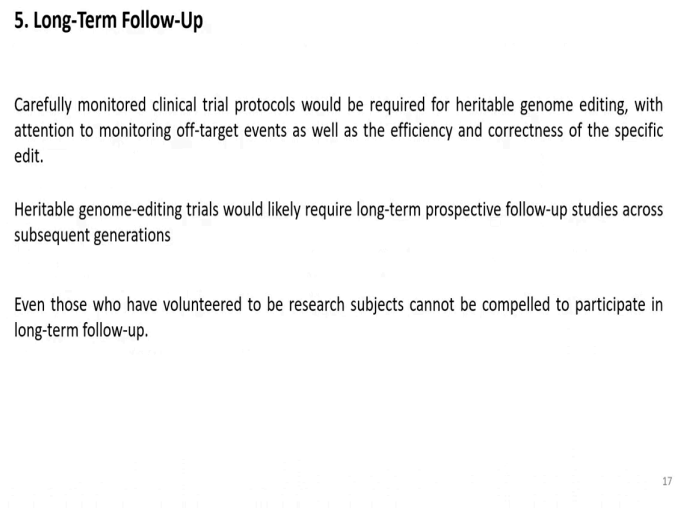

One important aspect is the long term follow up. Carefully monitored clinical trial protocols would be required for heritable genome editing with attention to monitoring off-target events as well as the efficiency and correctness of the specific edit and since humans are going to leave for around 60, 70, 80 years.

The team who monitors the people receiving the heritable genome editing has to be constantly changed with proper information being documented recorded and passed on as the team changes. Heritable genome editing trials would likely require long term prospective follow-up studies across subsequent generations. So, which makes the follow up rather more challenging even those who have volunteer to be research subjects cannot be compelled to participate in long term follow up however.

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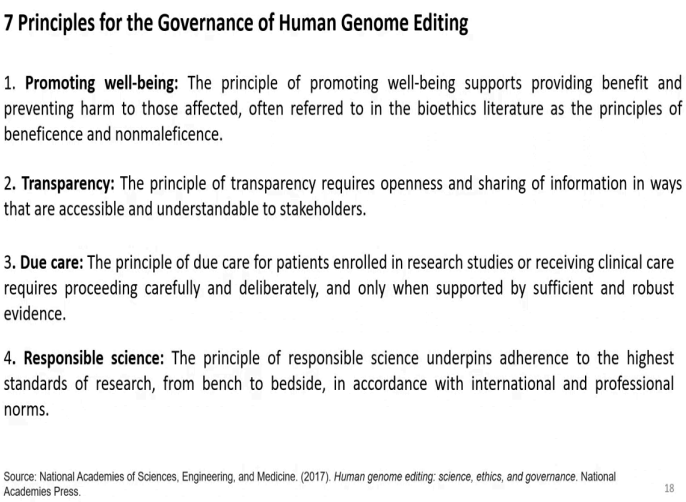

Principles for the governance of human genome editing: Number 1 is promoting well-being: The principles of promoting well-being supports providing benefits and preventing harm to those affected, often referred to in the bioethics literature the principles of beneficence and nonmaleficence. 2nd point is the transparency: The principles of transparency requires openness and sharing of information in ways that are accessible and understandable to stakeholders.

3rd is due care: The principle of due care for patients enrolled in research studies or receiving clinical care requests proceeding carefully and deliberately, and only when supported by sufficient and robust evidence. 4th is responsible science: The principle of responsible science underpins adherence to the highest standard of research from bench to bedside in accordance with the international professional norms.

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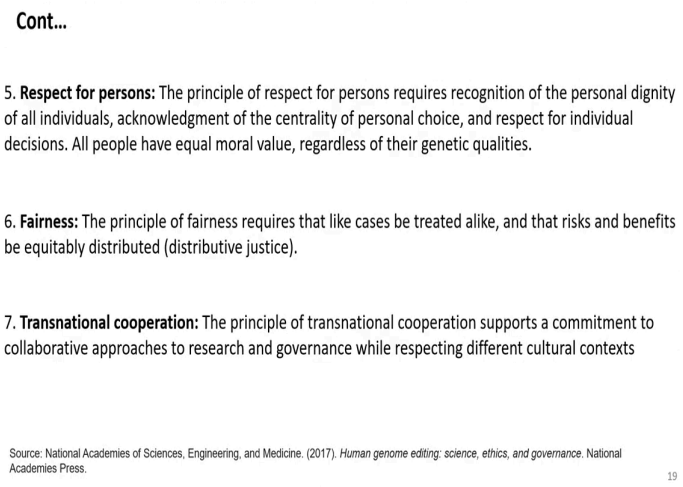

5th one is the respect for persons: The principle of respect for persons requires recognition of the personal dignity of all individuals, acknowledgement of the centrality of personal choice, and respect for individual decisions. All people have equal moral value, regardless of their genetic qualities. 6th principle is the fairness: The principle of fairness requires that like cases be treated alike, and that risks and benefits be equitably distributed which is also known as distributive justice.

The 7th point is translational cooperation: The principle of translational cooperation supports a commitment to collaborative approaches to research and governance while respecting different cultural context.

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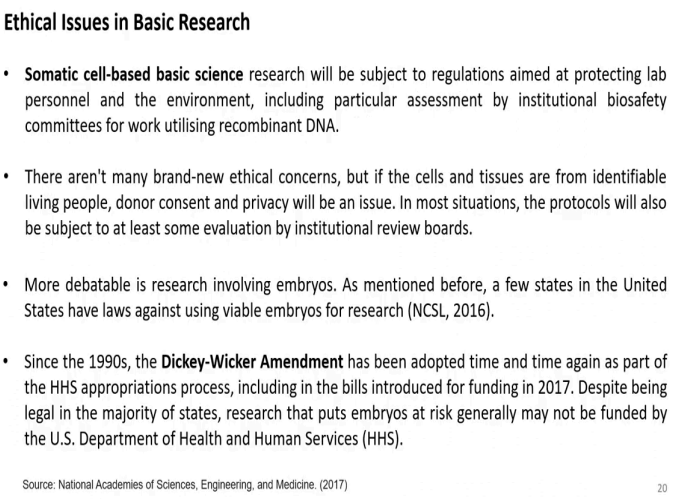

Let us not discuss about the ethical issues in basic research. Somatic cell based basic science research will be subject to regulations aimed at protecting lab personnel and the environment including particular assessment by Institutional Biosafety Committees for work utilizing recombinant DNA.

Research involving embryo is much more debatable as mentioned a few states in the United States have laws against using very viable embryos for a research. Since the 1990s the Dickey-Wicker Amendment has been adopted time and again as part of the Health and Human Services appropriation process, including in the bills introduced for funding in 2017. Despite being legal in the majority of states, research that puts embryos at risk generally may not be funded by the U.S Department of Human and Health Services.

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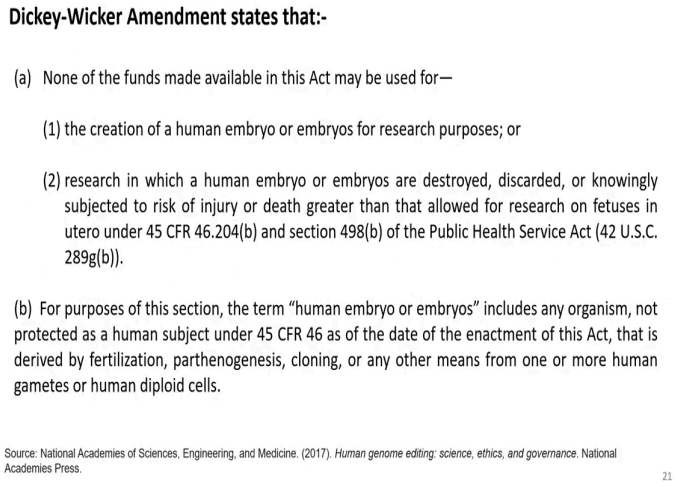

The Dickey-Wicker Amendment states that, (a) none of the funds made available in this Act may be used for the creation of a human embryo or embryos for research purposes or research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204 (b) and section 498 (b) of the Public Health Service Act 42 U.S.C 289g (b).

And number (b), for purposes of this section the term human embryo or embryos includes any organism not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning or any other means from one or more human gametes or human diploid cells.

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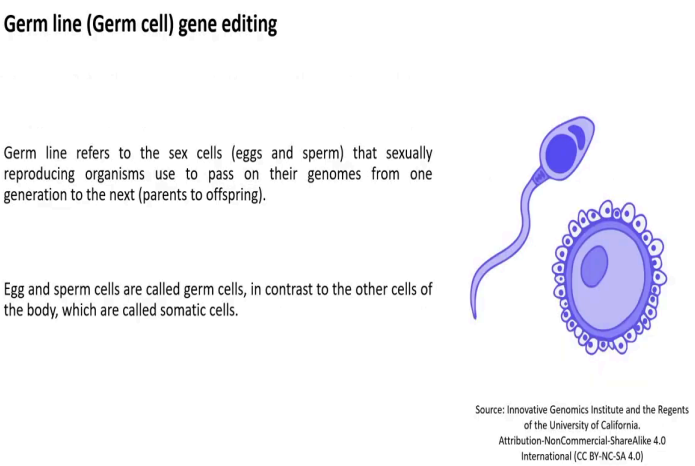

Germ line cell or gene editing germline refers to the sex cells like eggs and sperms that sexually reproducing organisms used to pass on their genomes from one generation to the next which is parent to offspring or vertical inheritance egg and sperm cells are called germ cells in contrast to the other cells of the body which are called somatic cells.

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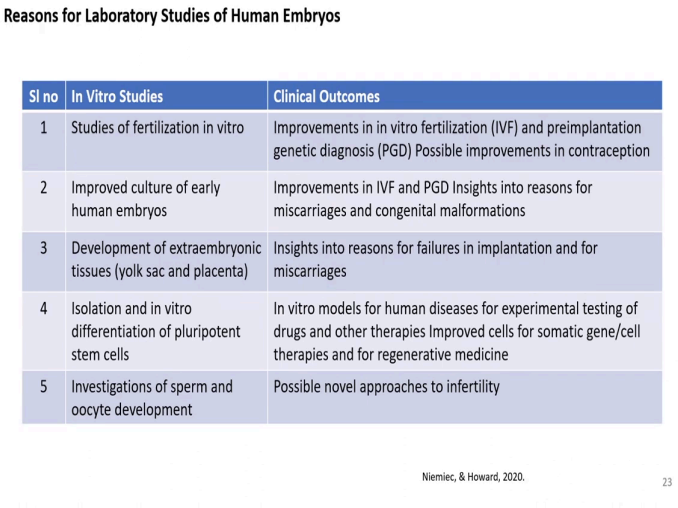

There are various reasons which have been justified for laboratory studies of human embryos for example, in vitro studies involving studies of fertilization in vitro is required for the improvements in vitro fertilization and pre-implantation genetic diagnosis (PGD) Possible

improvements in contraception improved culture of early human embryos will lead to the improvements in IVF and pre-implantation genetic diagnosis insights into reasons for miscarriages and congenital malformations.

Development of extra embryonic tissues will give us insights into reasons for failures in implement implantation and for miscarriages and isolation and in vitro differentiation of pluripotent stem cells will help us in building in vitro models for human diseases for experimental testing of drugs. And other therapies improved cells for somatic gene cell therapies and for regenerative medicine. Investigations of sperm and oocyte development will help us developing possible novel approaches to infertility.

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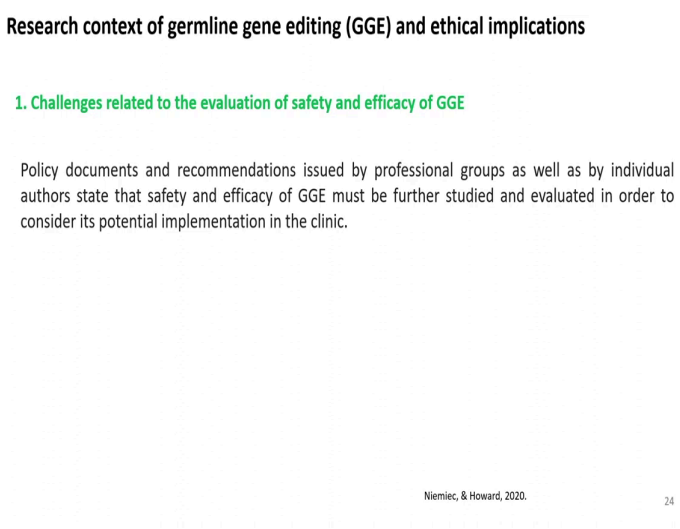

So, overall we can see that there are lot of advantages using human embryos for laboratory studies in solving many of the scientific challenges, but there are many regulations and ethical problems which has to be respected equally the research context of germline gene editing and ethical implications.

Number 1 is the challenges related to the evaluation of safety and efficacy of germ-line gene editing. Policy documents and recommendations issued by professional groups as well as by individual author state that safety and efficacy of GGE must be further studied and evaluated in order to consider its potential implementation in the a clinic.

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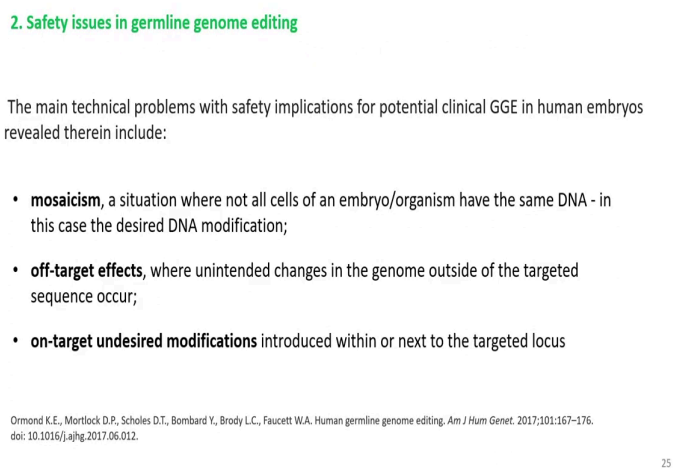

2nd issue is the safety issues in germline genome editing. The main technical problem with safety implications for potential clinical GGE in human embryos include mosaicism a situation where not all cells of an embryo or organism have the same DNA.

In this case the desired DNA modification off target effects where unintended changes in the genome outside of the targeted sequence may occur or occurs on target undesired a modifications also happen due to introduction within or next to the target locus.

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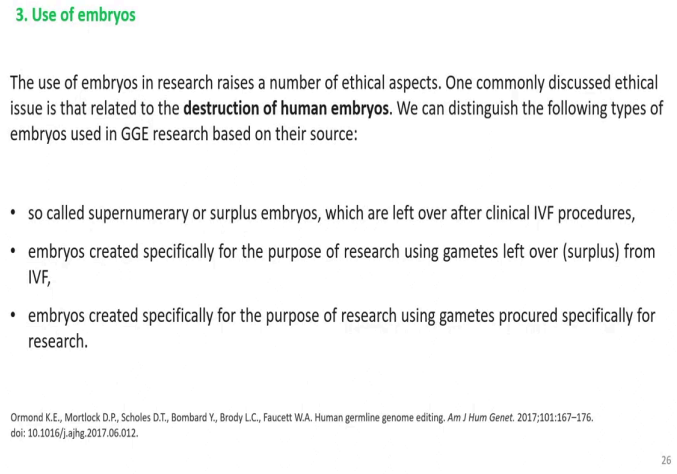

The 3rd issue is the use of embryos. The use of embryos in research raises a number of ethical aspects in spite of the promises we have discussed in the table.

One commonly discussed ethical issues is that related to the destruction of human embryos. We can distinguish the following types of embryos used in GGE research based on their source so, called supernumerary or surplus embryos which are left over after clinical IVF procedures embryos created specifically for the purpose of research using gametes leftover surplus from IVF.

Then embryos created or specifically for the purpose of research using gametes are procured specifically for research.

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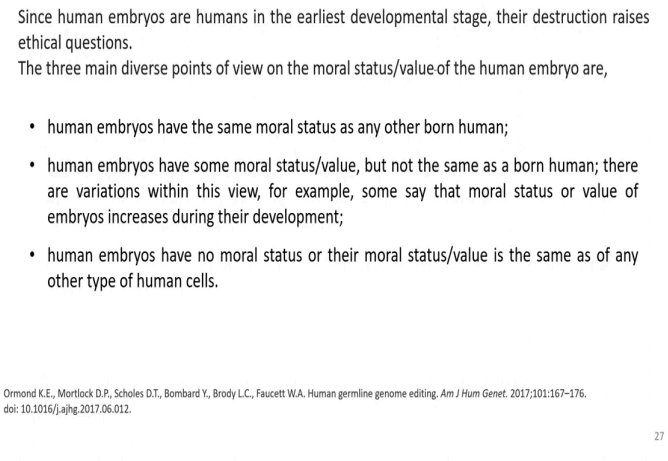

Since human embryos are humans in the earliest developmental stage their destruction raises ethical questions beyond doubt. The three main diverse points of view on the moral status or value of the human embryos being put across are number 1 human embryos have the same moral status as any other born human individual.

Another view is that human embryos have same moral status oblique value, but not the same as a born human. There are variations within this view for example; some say that moral status or value of embryos increase during their development. The third view is that human embryos have no moral status or their moral status value is the same of as of any other type of human cells, but not equal to the human.

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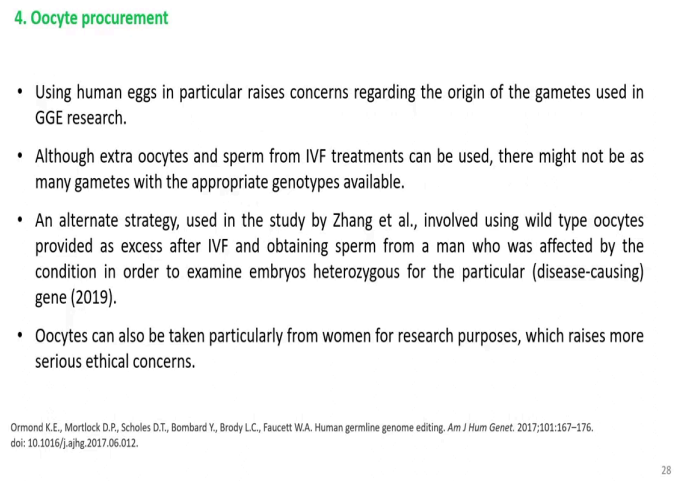

Another important issue is the oocyte procurement using human eggs in particular raises concerns regarding the origin of the gametes used in GGE research.

Although extra oocytes and sperm from IVF treatments can be used there might not be as many gametes with the appropriate genotypes available. An alternate strategy used in the study by Zhang et al involved using wild type oocytes provided as excess after IVF and obtaining sperm from a man who was affected by the condition in order to examine embryos heterozygous for the particular disease causing gene in 2019. Oocytes can also be taken particularly from women for research purposes which raises more serious ethical concern.

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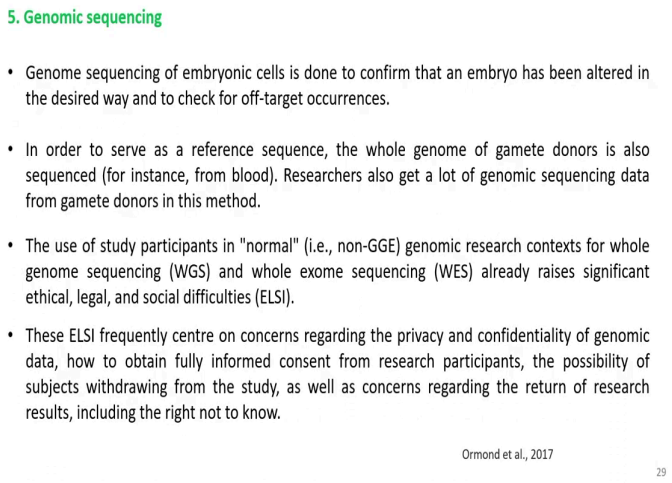

Genome sequencing is emerging as one of the important issues in the current era. Genome sequencing of embryonic cells is done to confirm that an embryo has been altered in the desired way and to check for off target occurrences in order to serve as a reference sequence, the whole genome of gamete donors is also sequence for instance from blood, researches also get a lot of genomic sequencing data from gamete donors in this procedure.

The use of study participants in normal that is non GGE genomic research context for whole genome sequencing and whole exome sequencing already raises significant ethical legal and social difficulties. These ELSI frequently centre on concerns regarding the privacy and confidentiality of genomic data how to obtain fully informed consent from research participants the possibility of subjects withdrawing from the study, as well as concerns regarding the return of research results including a right not to know.

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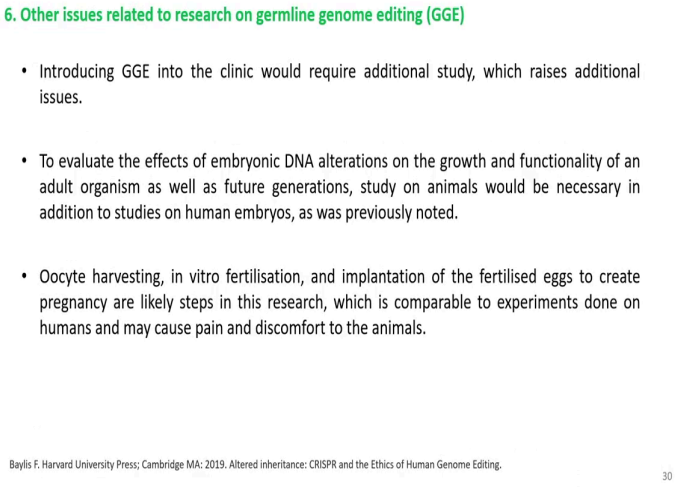

Other issues related to research on germline genome editing. Introducing GGE into the clinic would require additional study which raises additional issues to evaluate the effects of embryonic DNA alterations on the growth and functionality of an adult organism as well as future generations.

Study on animals would be necessary in addition to study on human embryos as was previously noted. Oocyte harvesting in vitro fertilization and implantation of the fertilized eggs to create pregnancy are likely steps in this research, which is comparable to experiments done on humans and may cause pain and discomfort to the animals. So, with this we come to end of part A of this lecture we will continue this lecture in part B.