TAKSHASHILA
INSTITUTION

DISCUSSION DOCUMENT
OCTOBER 2017

A FRAMEWORK FOR GOVERNING GENE EDITING

DISCUSSION DOCUMENT 2017-04

October 13, 2017

By
Madhav Chandavarkar
Anirudh Kanisetti
Shambhavi Naik
Ajay Patri

The Takshashila Institution
Bengaluru, India

This discussion document can be cited as "Madhav Chandavarkar, Anirudh Kanisetti, et al, *A Framework For Governing Gene Editing*, Takshashila Discussion Document, 2017-04".

Executive Summary

Gene editing offers many benefits. They range from basic research that can enhance the scientific understanding of gene functions to practical applications like improved healthcare and agricultural production. At the same time, like other developing technologies, gene editing is not without its limitations and problems.

Guided by a few core principles, this discussion document[1] develops a framework to analyse gene editing technologies. The paper explores three broad categories, corresponding to the stage of development of the technology: Fundamental R&D, Commercial R&D and Commercialisation. Each of these groups requires a different governance principle. This idea is used to develop a three-level framework, as set out below.

1. *"Laboratory" Stage (Fundamental Research)* – Compliance with Standards.
   Research organisations free to conduct lab experiments as long as they adhere to scientific standards and protocols for different technologies. Government to set standards in collaboration with research and industry groups.

2. *"Trial" Stage (Commercial R&D)* – Subject to Approval.
   Clinical/open field trials on a demonstrated product cannot be carried out without prior approval. The approval will be granted by an agency based on standards set by the government in collaboration with research and industry groups.

3. *"Public Release" Stage (Commercialisation)* – Verification of Safety.
   Product can be sold on the market only after government has independently verified that the product meets safety and disclosure standards.

A vital feature of this framework is that there is *no absolute moratorium on any technology*. Instead, it provides for safety checks at each stage which become increasingly rigorous as the technology/application gets closer to being released to the public. Its primary goal is to ensure that the regulatory environment is conducive to scientific progress. As such, the framework would allow India to harness the benefits of gene editing while keeping risks in check.

The implementation of such a framework, which separately regulates laboratories, trials and public releases of gene editing technologies could take many forms. One such form would be the creation of independent accreditation firms that would implement safety standards at the Laboratory Stage and approve the trials of gene editing research. These safety standards as well as the parameters on which approvals are granted would implement standards set by a Gene Editing Authority. This authority would also be in charge of setting safety protocols for laboratories and regulating the public release of gene edited products. This framework allows timely approvals while still keeping risks in check. However, a detailed discussion of implementation pathways is left for future work.

[1] This document is prepared for the purpose of discussion and debate and does not necessarily constitute Takshashila's policy recommendations. To contact us about the research, write to research@takshashila.org.in.

Introduction

Gene editing is the process by which genes are altered, which in some cases may lead to changes in the characteristics of the cell/organism. This process occurs in nature – every time a cell divides, there is a chance (although very low) for gene editing to take place – enabling species to evolve by passing on beneficial traits. However, natural gene editing is slow as noticeable changes can take decades.

Scientists have been using gene editing to explore gene functions in laboratories since the early 1990s. These gene editing technologies were inefficient and expensive to produce, and were also risky because they involved forcibly adding in an extra gene sequence from a different organism into the genome. But recently a new technology was developed called CRISPR-Cas9 that could allow the same end effects without bringing in foreign DNA, alleviating at least some of the concerns that genetically modified organisms ("GMOs") have raised. The CRISPR technology is not only far more accurate, but also considerably cheaper than existing technologies, which has accelerated discussions about the regulation of gene editing.

This regulation is an thorny issue as gene editing, along with artificial intelligence and automation, is potentially one of the most disruptive and controversial technologies of the 21st century. Its potential benefits, which range from medical treatments to agriculture, make a compelling case for the technology. But gene editing is still a developing technology that is yet to iron out its imperfections. Arguments against gene editing range from fears of its impact on the environment to deeper ethical questions, such as the consent of future generations when editing human genes. It is imperative that these considerations are factored before determining the ideal regulatory approach to what is potentially an extremely beneficial technology. The need for such an endeavour is especially pronounced in India, where the applications of biotechnology, specifically gene editing technology, remain largely underutilised.

Section I of this paper begins by describing why gene editing should be allowed but at the same time outlines the need for oversight. Section II contains a list of core principles that were determined as being the ideal guide to regulating gene editing. Section III is the principal section of the paper and contains a broad framework for regulating gene editing in India. It begins by providing an analytical framework to assess the various types of gene editing applications on two grounds: the risk of unintended consequences and the ethical considerations inherent in their use. The types of gene editing applications are categorised on the bases of the type of organism edited, and the stage of research and development reached. After the various types of gene editing applications were assessed, three broad categories were outlined which form the base of the governance framework proposed. Section IV describes how gene editing research on humans, plants, and animals should be regulated differently at the laboratory, trials, and public release stages. Section V explains how some of the typical concerns about gene editing are dealt with by this framework. Section VI describes why it is in India's national interest to adopt this framework. The conclusion is followed by Appendices that buttress many of the arguments made in the main paper.

1. The Need for a Governance Framework

Research into the editing and manipulation of genes editing is not a recent phenomenon, and from the beginning, it has been plagued with concerns about its governance. This can be seen from the International Congress on Recombinant DNA Molecules in 1975 (the Asilomar Conference), where a host of scientists, lawyers and physicians debated how the field was to proceed amongst scientific fears of biohazards and general concerns from the public. The Asilomar Conference took a precautionary approach that graded different applications on their risks and was crucial in paving the way for a variety of beneficial research and technologies to be developed[1].

A similar inflection point has been reached with gene editing. The leaps in the accuracy, effectiveness and costs of gene editing brought about by CRISPR have ensured that CRISPR products have already found their way into the markets. As we move forward, a new discussion needs to be had around gene editing and its applications that will repeat the success of the Asilomar Conference in allowing a new technology to flourish. This debate should look at both the worth of gene editing technologies in the uses they can potentially be put to as well as the risks and limitations.

1.1. Gene editing offers overwhelming benefits

Gene editing is a controversial technology which many people are opposed to on both scientific and ethical grounds. While these concerns warrant regulatory oversight of some kind (as will be discussed), they need to be contrasted with the potential benefits that gene editing technology offers. These include better medical treatments, creating varieties of crops and animals with beneficial traits such as resistance to pests and diseases (making production cheaper) or simply for scientific understanding (the best way to understand gene functions is to edit genes). The various benefits of gene editing are described in greater detail later but for now it is sufficient to state that they are numerous and varied, and more importantly can address many of India's problems[2]. India still imports a large proportion of its food, resulting in a negative balance of trade. But gene editing has the potential to address this issue through varieties that decrease production costs or increase yields. Healthcare is also a significant concern that gene editing could help address as the technology could help prevent a host of diseases and thus reduce the burden on already strained healthcare services.

These potential benefits gene editing technologies may eventually overwhelm any objections to the technology as an increasingly populated and climate-change afflicted Earth struggles to provide food and other natural resources. While that may be conjecture, it is highly likely that more people will avail gene edited products in the future given their already prevalent use.

1.2 It is a nascent technology

Gene editing is a relatively recent technology, and is therefore far from being precise. For instance, there are still many gaps in the understanding of which gene sequences determine which traits and how – a prerequisite for any gene editing. Even when it is understood, there are two considerable risks with the gene editing itself: off-target effects (where the editing affects cells not specifically targeted[3]) and mosaicism (where the edit does not evenly affect the targeted cells[4]).

Some of these risks can be attributed to the method of earlier gene technologies to forcibly add an extra gene sequence from a different organism into the subject genome. But the CRISPR-Cas9 system, which does not use this method and is considered extremely accurate in comparison, has not been able to entirely eliminate these risks.

1.3. Due care and caution is required

There are many concerns about the use of gene editing that are independent of the precision of the technology. For example, the environmental impact caused by the introduction of just one gene edited organism may result in a host of undesired consequences that could disrupt biodiversity and ecosystems such as a gene edited organism replacing an indigenous variety. There are also significant ethical questions brought up by the use of gene editing. These include questions on equal access or the ways in which the editing of human genes respects individual autonomy of subjects such as protecting confidentiality or obtaining free, prior and informed consent. Both the science and the ethical concerns come to a head when gene edits are done on reproductive cells and are therefore hereditary. The intergenerational effects of such edits are still not understood and subsequent generations have gene edits to which they have not consented to[5].

It can be seen that gene editing has a sufficient amount of externalities that warrant a government intervention of some kind. However, this intervention must not stifle the growth of the industry, and should instead ensure that the harms are minimised and benefits maximised. A rigorous debate should be conducted between policy makers, scientists and the public at large to determine the ideal form of this government intervention. A similar endeavour was recently conducted by the US Congress before it passed the SELF Drive Act to regulate the new and disruptive technology of self-driving cars[6].

Though an Asilomar 2.0 was conducted recently[7], the landscape of biotechnology is drastically different now[8] and it has not had the same impact on public discourse as its predecessor, at least not yet. In any case, it is prudent for India and its scientists to first determine what approach best serves Indian national interests before committing to international agreements on the issue. The need for this is pressing; though there are currently very few binding international agreements on gene editing, this will likely change and India must be able to contribute to the formation of any regulatory framework.

2. Guiding Principles

Now that the need for both allowing gene editing as well as regulating it is established, the question of what form this regulation should take becomes paramount. In order to determine the answer, it is necessary to outline a few core objectives to serve as guiding principles for any regulatory framework. After due consideration, the following principles were determined to best guide a gene editing policy for India:

2.1 Scientific progress must not be inhibited by regulations

There are two compelling reasons for encouraging scientific progress. The first is that the pursuit of scientific knowledge has generally led to an improvement in human welfare. The second is that nations can ill-afford to shun scientific progress in a globalised and interconnected world since doing so can come at the risk of losing a competitive edge in economic and military advancement.

Therefore, unless there is compelling reason to do so, it is wise to not inhibit scientific progress. India already has a biotechnology industry that is beginning to work in this area and it is important that it is allowed to flourish in a conducive environment in its early stages.

2.2 A technology and its applications should be viewed separately

An argument can be made in favour of considering the pursuit of scientific knowledge as an inherently moral exercise[9]. A distinction should be drawn between the pursuit of knowledge and the ways in which such newfound knowledge can be put to use. In other words, while the application of scientific knowledge might have adverse effects, the knowledge itself cannot be branded undesirable. As a result, scientists must be given the freedom to conduct research, even if its applications push the boundaries of what is currently known and accepted. This is particularly so in the context of CRISPR, which is a technology still in its nascent stages, with vast potential to provide benefits in the future.

2.3 Regulation is better than outright prohibition

There have been calls for a complete moratorium on certain applications of genetic engineering, as discussed in the paper. Such blanket prohibitions will not only be difficult to enforce but are likely to drive the industry underground or to nations with lax oversight. Therefore, it is more prudent to have a framework of regulations with appropriate checks and balances that permits continued research and development of gene editing than one that bans it outright. These regulations should be primarily based on preventing harms whether physical or ethical but more importantly must not be so onerous as to choke the industry.

2.4. Global and national interests must be balanced

There are many issues with how gene editing technologies are used and disseminated on a global scale such as the trans-border impact on ecosystems or the international mechanisms through which nations share patents on genetic materials. At the same time, gene editing is also capable of addressing major domestic policy problems like healthcare and food security. Any approach to gene editing technologies must thus balance these global and national interests in order to be feasible. This is particularly the case with developing nations such as India as they must protect their national interests from developed nations that have developed a majority of gene technologies and have greater negotiating power. Given the likelihood that the technology will play a crucial role in an increasingly populated world India should take a proactive stance in developing national and international policy.

2.5. Policymaking must be scientific and inclusive

Gene editing, like any other line of scientific enquiry, is not only a highly technical field but one that is rapidly evolving. Scientists are the most likely to understand the limitations and applications of any given gene editing technique and are thus best placed to determine the optimal path for further development and regulation. Therefore, they must be given primacy in determining the contours of any regulatory framework.

However, given the far-reaching impact of gene editing as well as its ethical complexities, the views of other stakeholders such as farmers, the disabled, and medical professionals, must still be taken into account when framing any gene editing policy.

3. Arriving at a Governance Framework

Before determining a governance framework it is necessary to first understand the peculiarities of various gene editing technologies as a one-size-fits-all approach will not be feasible. As such, an analytical model that categorises gene editing technologies on the bases of the type of cell being targeted and the stage of research is proposed. These categories will then be assessed on the bases of the scientific and ethical risks involved in their use, with each of these considerations forming the axes of the model.

A visual representation of the analysis is presented below and is followed by an explanation as to how the conclusions were reached.

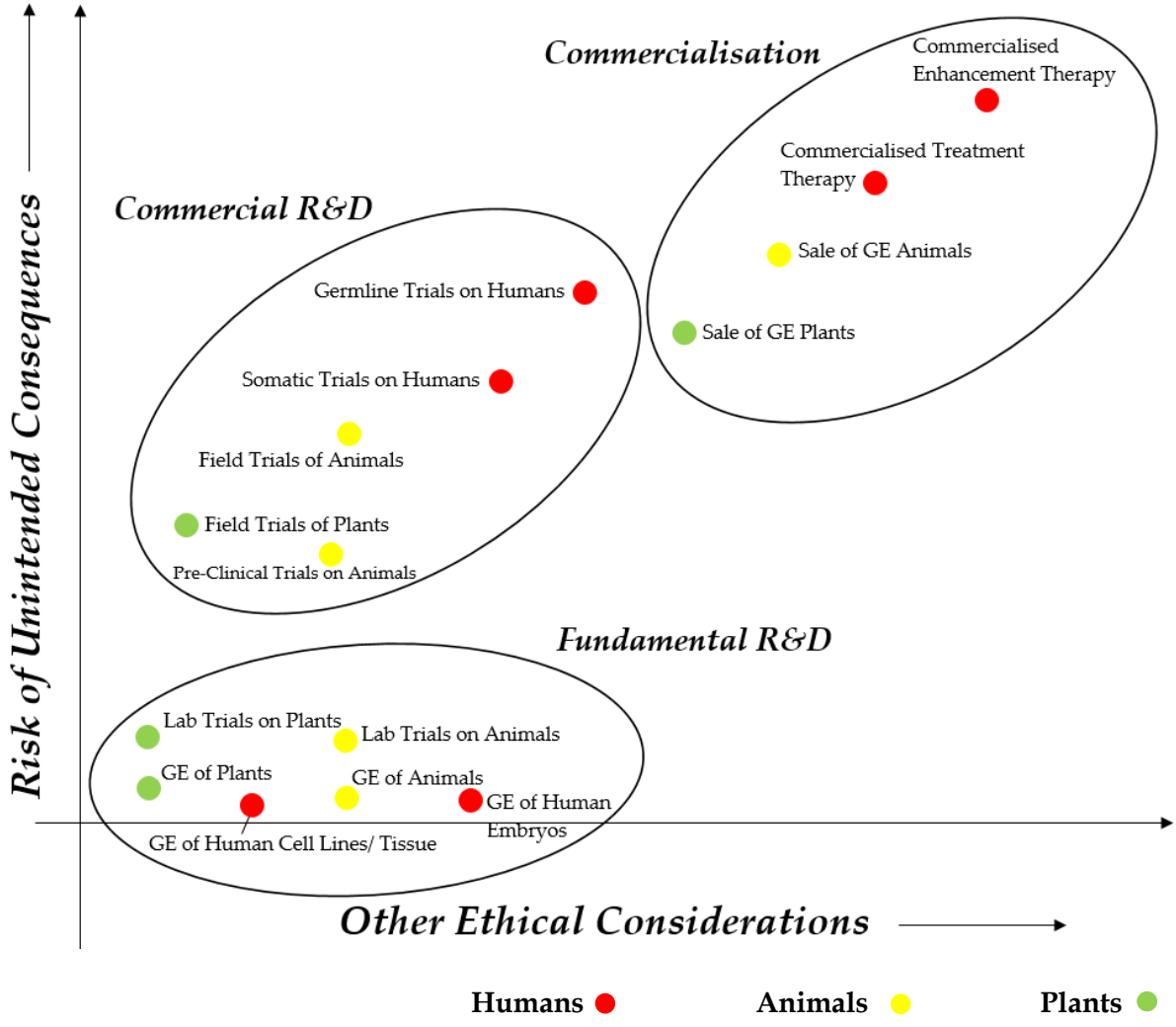

Figure 6.1. *Classification of Gene-Editing Technology Applications.*

The ethical questions of using gene-editing technologies cannot be easily separated from scientific risks. For example, the risk of unintended adverse environmental impacts - such as the destruction of an indigenous variety of a plant by an edited version - also involves the ethical question of considering the environment sacrosanct. A delineation of these two risks is consequently necessary in order to ensure that the two axes are separate and therefore workable.

3.1 Risk of Unintended Consequences

This axis represents *scientific* risks and contains the unintended consequences that may result from the use of gene editing. As the name suggests, these are *consequentialist* considerations, that is to say, considerations about the consequences of *using* gene editing. Examples of such considerations would be:

1. The impact on human well-being. For example, gene edited crops may impact allergenicity[10].
2. Environmental impacts. For example, the impact of monocultures and outcrossing on ecosystems[11].
3. Impacts on inequality. This may be separated into societal and economic inequality and genetic inequality.
4. The economic impact on farmers brought about by the cultivation of genetically edited crops.

The primary reason for considering unintended consequences separately is that they can be addressed (at least theoretically) using regulations and laws. For example, stringent testing and approval requirements similar to those required for pharmaceutical drugs would address, or at least minimise, negative impacts on the environment and human beings. Appendix B discusses these scientific risks in greater detail.

3.2. Ethical Considerations

This axis represents the ethical considerations inherent in the use of the technology such as questions of consent, or whether humans should tamper with the "order of nature". As such, they are *non-consequentialist* considerations, which involve ethical questions inherent in the human *use* of gene editing itself. For example:

1. Is the human genome so sacrosanct as to protect it from editing?
2. Is gene editing artificial, unnatural, or against the order of nature? (The "playing God" argument)
3. Does gene editing to treat disabilities and diseases in humans violate the rights of the disabled?
4. How does gene editing sit with a general respect for individuals and life at large?
5. Does genetic editing which confers hereditary traits (germline editing) violate the autonomy of subsequent generations without their consent? (intergenerational equity)

Many of these questions are deeply philosophical and **cannot** be addressed solely by regulations and laws as they require value judgments (which may then may be enforced through laws). A more detailed discussion of some of these considerations can be seen in Appendix C.

3.3. Categorisation of Gene Editing Technologies

In order to populate this model, a categorisation of gene editing technologies was developed as the scientific risks and ethical considerations vary between different types of gene editing. The following two bases are used:

3.3.1. Methodology of Categorisation

1. Type of Organism

The most obvious way in which to categorise the applications of gene editing would be to split them on the basis of the type of organism being edited. The reason for this is that the level of objections over ethical considerations differs drastically with the three outlined categories:

A. Plants

The gene editing of plants is the least controversial of the three categories, which may explain its comparative ubiquity. Though there are certainly many objections and controversies, the potential of gene edited plants to deal with policy problems like food security (by creating pest-resistant or high yield crops) have accelerated the application of gene editing on plants.

B. Animals

Aside from the obvious difference of the type of organism being edited, this category is much the same as plants as the primary application of gene editing in both is agricultural production. The major differences are that the protection of endangered animals is often prioritised over endangered plants (by the public) and that gene editing of animals has the additional ethical consideration of humane treatment.

C. Humans

Needless to say, concerns about the scientific risks and ethical considerations of gene editing are significantly amplified where the human genome is concerned. Many of the ethical considerations such as protection of autonomy and the sanctity of the human genome are only applicable with the case of humans. In fact the former concern requires editing of human genomes to be split further depending on the type of cell being edited.

a. Somatic Editing

Any editing done on the non-reproductive cells of an organism so that the modification is not passed on to subsequent generations, is known as **somatic** gene editing. The effects of somatic gene editing are limited to the cell type edited. For example, in the case of somatic editing of hematopoietic stem cells - cells that give rise to blood cells - only blood cells will possess the edited genome.

b. Germline Editing

Any editing done on reproductive cells or in an embryo, which *can* be passed on to future generations is known as **germline** editing. The effects of germline editing will be inherited by all cells formed from the original edited cell. With the example of blood cells, if the gene is edited in an embryo or a reproductive cell, all cells arising from this cell - skin, blood, brain, organs - will carry the edited gene. There is thus a greater risk of side-effects with the use of germline gene editing as well as additional ethical considerations regarding the autonomy of subsequent generations.

2. The Stage of Development

It is necessary to take cognisance of the life cycles involved in the conduct of genetic research as the level of scientific risks increase as research moves towards a final product. The following three basic stages are proposed:

A. The Laboratory Stage

The first step in conducting any genetic research is to understand the gene sequences and functions. This research needs to be conducted in the sterile environment of a laboratory. Once the gene sequences in play are understood further laboratory research in the form of trials would also need to be conducted to determine and perfect the best approach to editing the genes in order to achieve the desired results.

B. The Trial Stage

Once an approach is identified it will need to be tested on research subjects outside the laboratory but in a controlled environment. With human genetic applications this will first involve a pre-clinical trial on an animal and then a clinical trial on a human, while plant and animal applications will require a field trial.

C. The Public Stage

It is only after the completion of trials, where the viability, efficacy and safety of the specific gene editing technique has been determined, that the question of a public release can be considered.

Using a combination of these two bases, three broad categories of gene editing applications were determined: **Fundamental R&D**, **Commercial R&D** and **Commercialisation**. A brief discussion of each category and how it fares with the scientific risks and ethical considerations is outlined:

3.3.2. The Three Categories of Gene Editing

1. Fundamental R&D

Any genetic research that is carried out solely to further the understanding of a biological process without the obligation of developing intervening technologies would fall into this category.

Such research is characterised by small-scale experiments in the controlled settings of a laboratory making the risk of unintended consequences low. The ethical considerations vary on the basis of the area of research. Research on plants has minimal ethical considerations while research on animals only differs with the additional constraint of humane treatment.

Human genetic research in this category is be limited to editing of tissues and embryos (*without* implantation). This lack of human subjects make the ethical considerations of this group comparatively lower though issues of consent make the study of human embryos more complicated.

Fundamental R&D needs to be further separated into the sub-categories on the basis of the risk of unintended consequences:

A. Basic Genetic Research

The primary purpose of basic genetic research is to investigate gene functions through the editing of cells. A non-exhaustive and illustrative list of examples categorised on the basis of their applications is provided below:

- **Editing of Plants**: Studying gene functions in vivo (in whole plants) or through tissue culture, and preliminary tests into creating gene edited plants.
- **Editing of Animals*:*** Studying gene functions in live animals, and preliminary tests into creating gene edited animals. This also includes animal models of human conditions (such as cancer) to confirm gene functions.
- **Editing of human cell lines/tissues*:*** Studying gene functions in cell lines or tissue derived from humans.
- **Editing of human embryos (without implantation):** Experiments on human embryos from IVF centres for studying gene functions in development or to establish the safety of gene editing technologies and study any side-effects. These embryos are to be terminated without implantation.

B. Lab Trials

Once basic genetic functions of individual cells in multicellular organisms are understood well enough to be successfully edited, the next step is to see if these cells can be successfully edited in the organism. This would require lab trials where scientists attempt to create gene edited plants and animals. Though this may seem to raise more ethical considerations, it is fundamentally no different from editing

individual cells. However, the risk of unintended consequences is much higher when specific cells of complex organisms are edited.

- **Editing of Plants**: Growing gene edited plants and testing for gene expression.

- **Editing of Animals***:* Growing gene edited animals and testing for gene expression. Such research is limited to preliminary tests for generating such animals and studying genetic retention over a limited number of generations.

2. Commercial R&D

The term of "commercial" for this category is a misnomer, as it may be conducted by government entities as well, but it is used here to describe any research that is carried out with the specific *purpose* of developing commercial or clinical outcomes. The primary purpose of commercial R&D is to determine the viability, efficacy and safety of the gene edit outside the sterile environment of a laboratory.

As such, it is characterised by larger-scale experiments or trials performed in an open environment (with some controls), to examine the interaction of gene edited organisms with.

Since the very purpose of these trials is to test for any unintended consequences, the risks are much higher than those in Fundamental R&D. However, the scale of Commercial R&D trials is limited, and is akin to a pilot study. However, the ethical considerations will differ based on the purpose of the research.

1. Gene Editing of Plants and Animals (Field Trials)

   Field trials are conducted to assess the safety and validity of claims of gene edited plants and animals across generations, as well as to examine their efficacy outside a laboratory, and determine their interaction with the environment. It is only the possibility of unintended consequences that is increased, as field trials here do not differ from lab trials ethically speaking.

2. Gene Editing of Humans

   Trials for the genetic editing of humans have two stages as the presence of human subjects always amplifies concerns about ethical considerations as well having scientific risks.

   a. Pre-Clinical Gene Trials

   The testing of intended human interventions is so onerous that the technology must first be tested on animals (such as rats, dogs, pigs or primates) before proceeding with clinical trials on humans. These are generally performed after adequate laboratory research is done to prove the effectiveness on human tissues. Pre-clinical gene trials are performed in laboratory environments so there are low chances of unintended consequences, while the ethical considerations are similar to those involved in animal experimentation in general.

   b. Clinical Trials (Somatic and Germline)

Once the gene editing technology reaches a reasonable level of certainty and safety established by pre-clinical trials it is then tested on human subjects.

Clinical trials bring up multiple ethical considerations but the most important are probably issues of autonomy (such as consent and confidentiality) and the possibility of exploitation.

The difference between somatic and germline clinical trials on human subjects also changes the dynamics as germline clinical trials on implanted embryos have increased ethical considerations (consent) and unintended consequences (since the effects of the edited gene during the development and subsequent life of the child would be unknown).

3. Commercialisation

This category represents the final step of development, where gene edited products are made available for use outside a laboratory or controlled setting. If the release of the edited organism or editing technique is widespread, the possibility of unintended consequences is at its highest due to the sheer scale of its interaction with environment and society. After all, it is only at this scale that certain consequences (like the economic impact of the technology) really come into play. If the editing technique itself is made available, then ethical considerations are also very high as it could be used without sufficient caution and regard for individual autonomy. This category has the four following components:

- **Sale of GE Plants*:*** Commercial sale of gene edited plants.
- **Sale of GE Animals*:*** Commercial sale of gene edited animals.
- **Commercialised treatment technology*:*** Gene editing technologies aimed at treating pre-existing medical conditions in humans.
- **Commercialised enhancement technology*:*** Gene editing technologies aimed at selecting and/or enhancing human attributes such as intelligence and muscle strength.

4. The Three-Level Framework

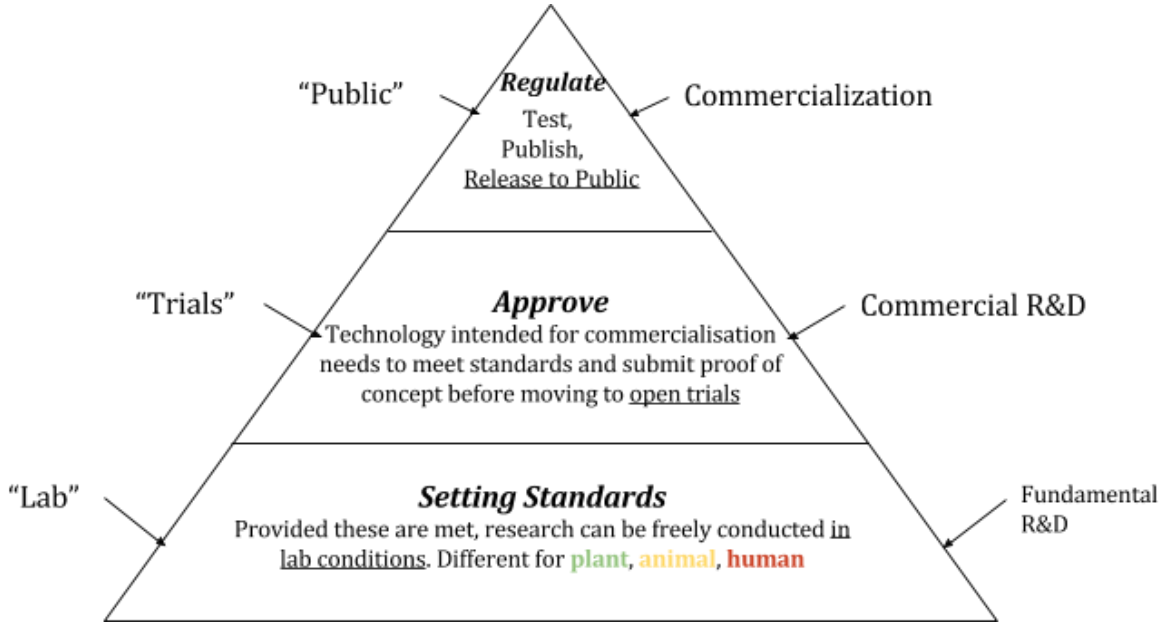

Figure 6.2. *The Three-Level Framework.*

It is proposed that the best way in which to ensure the safe progress of gene editing technologies in India will be to **create a regulatory framework conducive to strategic incrementalism in biotechnology research**. This framework should be based upon the analytical model outlined, with layered regulations that are more rigorous for the comparatively risky stage of Commercialisation than they are for Fundamental R&D. This proposed environment aims to minimise government interventions while still ensuring high standards of safety and reduction in the chances of unforeseen side effects. The aim is to encourage plenty of incentivised, competitive players in the Indian market who are not hamstrung by onerous or expensive regulations.

For plants and animals, each of the stages outlined above needs to have the following:

1. **"Laboratory" Stage - Standard Setting - Corresponds to Fundamental R&D.**

   As both the risk of unintended consequences and ethical considerations are low this stage requires minimum regulatory oversight. The only regulations should be the setting of rigorous scientific and academic standards, and as well as tailored safety protocols for different gene editing technologies, to which research laboratories must adhere. As long as they adhere to these standards and protocols, laboratories should be free to conduct gene editing research without requiring prior approval.

2. **"Trial" Stage – Approvals - Corresponds to Commercial R&D.**

   The risk of unintended consequences is considerably higher outside the controlled environment of a laboratory.

As such field and clinical trials should be compulsory before exposure to the environment. Proposals of such trials should be sent for approval before they commence, in order to make sure that they are being conducted in a appropriate environment and meet other such pre-conditions[12]. This stage will ensure that a product or technology that is not yet fully developed or understood is not tested in a manner that risks causing potentially irreversible damage.

3. **"Public" Stage - Regulations - Corresponds to Commercialisation.**

The ethical considerations and scientific risks at this stage are at their highest when a gene edited product or gene editing technique is widely utilised. Once gene edited products are found to be viable enough at the trial stage to move towards commercialisation, an additional layer of independent, transparent, time-bound tests should be conducted before the product can be widely released[13]. The purpose of these tests is to independently verify the results of the trials as well as function as an additional check to confirm that the product is not harmful to the environment or the public. The standards, protocols, and final approvals at this stage should be considerably more stringent than others as any unintended consequences will be considerably harder to reverse.

4.1. Human Interventions

This same framework should also be applied towards the development of gene editing applications for human interventions but with suitable modifications and additional requirements:

1. **"Laboratory" Stage**

The scientific standards and protocols for conducting gene-editing on human cells will differ from those for research on plants and animals and should be stricter and more onerous. While embryos may be edited, experiments upon live humans will fall under the trials stage. It is also proposed that an additional layer of approval with more stringent precautions should be kept for experiments involving embryos and germline editing in light of their strong ethical considerations and ramifications.

2. **"Trial" Stage**

The research proposal should show a clear link between the gene being edited and the projected outcome. Approvals for clinical trials of somatic therapies should be subjected to prior satisfactory and peer-reviewed research in cell lines, human tissue and pre-clinical animal models. For germline editing interventions, a layered incremental trial system is suggested – which would begin with germline editing without implantation and end with germline editing with implantation with an increasing number of enrolments.

3. **"Public" Stage**

Release the product only after intensive clinical trials and an understanding of its inter-generational effects, plus independent, transparent, time-bound tests to

independently verify the results of the trials & confirm that the product is not harmful to the environment or the public.

A summary of the framework, with the differences for organisms, is presented below.

Target/Stage	*Lab*	*Trials*	*Public*
Plants & Animals	Setting of rigorous scientific and academic standards, and as well as tailored safety protocols for different gene editing technologies	Open trials should first be approved, in order to make sure that they are being conducted in an appropriate environment and meet other such pre-conditions	Independent, transparent, time-bound tests to independently verify the results of the trials & confirm that the product is not harmful to the environment or the public.
Humans	Stricter and more onerous standards. Additional layer of approval with more stringent precautions to be kept for experiments involving embryos and germline editing. No experiments on live humans.	*Somatic* trials should be approved after prior satisfactory and peer-reviewed research in cell lines, human tissue and pre-clinical animal models. For *Germline* trials - a layered incremental trial system, starting from editing without implantation and ending with implantation, with an increasing number of enrolments.	Release the product only after intensive clinical trials and an understanding of its inter-generational effects, plus the above tests.

Additional Notes on the Three Level Framework

- Violators of the standards should be subject to penalties defined by law. A set of broad non-binding guidelines as established by the ICMR are not enough.

- The standards set for the three levels should **evolve** continually as more advanced technologies and applications are found.

- Scientists, bioethicists, domain and industry experts, members of the executive and judiciary, and some consumer organisations need to be consulted regarding the evolution of the standards.

4.2. Possible Implementation Pathways

The Three Level Framework can be implemented in many ways. One possible route would be to set up an independent statutory regulatory body responsible for all three stages which would look at each proposal and product in a case-by-case manner. The peculiarities of varying gene editing technologies as well as the rapid rate of progress in the field would necessitate such a granular approach but ensuring timely approvals and tests may be difficult.

Independent Accreditation Firms

A more comprehensive way to ensure timely testing and approvals would be to allow the creation of Independent Accreditation Firms (IAFs) for independently testing safety standards as well as approving trials of gene editing technologies. These IAFs would then, in turn, be regulated by a centralised authority. This would increase the efficiency of the regulatory framework as the quantity of these firms would facilitate timely approvals for laboratories but still be lesser than the number of proposals a governmental approval agency would have to regulate. In order to prevent conflicts of interest, there should be two kinds of IAFs: those that verify safety standards of laboratories and those that approve trials.

Gene Editing Authority

This proposed centralised authority, or Gene Editing Authority (GEA) as it were, would be in charge of setting the standards, protocols and guidelines that the IAFs would then apply. This would probably take the form of an objective testing methodology with minimum standards that would ensure the safety and veracity of candidates' proposals on a case-by-case basis. Different sets of approvals could be stipulated by the GEA for different technologies. For example, a genetic therapy for humans would require a different set of approvals compared to a genetically modified crop. The GEA would also conduct an independent verification of the safety and veracity of a proposed gene editing application before it is released for widespread use at the Public Stage. Though this process may be faster if conducted by an IAF, the possibility of conflicts of interest would prevent an additional verification from being truly independent. Given that the primary purpose at this stage is to prevent irreversible consequences, a slower and therefore more cautious process is a worthwhile trade-off as it allows consultation with ecologists and physicians on potential impacts.

Given the highly technical and fast-moving nature of gene editing great care should be taken in the drafting of the law creating this framework, especially with the definitions. If the language of the legislation is too broad and overreaching it could restrict research and applications of biotechnology that fall outside the controversies of gene editing. Conversely, if the language is too specific, it could quickly be made redundant by advancements in the technology. The implementing legislation should therefore, to the utmost extent, contain principles and enable the GEA, with due public input and oversight, to set the exact contours of how they are to be implemented.

As such, the composition of the GEA becomes crucial. Ideally, it should be comprised of core specialists with domain expertise. This would include scientists well versed in genetics, microbiology and biotechnology, environmentalists, ethicists, and lawyers. The IAFs should also have a similar composition with the addition of representatives from a project specific component such as a relevant consumer group. To ensure that the conduct of the GEA and IAFs are led by scientific principles, it is recommended that the chairman of both be a scientist.

The utilisation of private firms will also necessitate the creation of a separate grievance and redressal committee to deal with transgressions committed by both IAFs as well as researching institutions. This committee should consist of a panel of experts (scientists, ethicists, lawyers) who can review grievances arising from the use of gene editing technologies. This committee should be a quasi-judicial authority that has the power to summon witnesses, revoke approvals and where necessary issue punishments.

A robust regulatory framework will also become increasingly necessary as gene editing technologies advance in order to combat the emergence of spurious treatments. CRISPR is likely to lead to such treatments and ideally claims of the use of CRISPR technology for gene therapy, should have a clear validation from the ICMR before being applied to any patient and with strict punishments for offenders. This has been a problem with stem cell therapy being promoted by miscreants and quacks for commercial profit and such practices should be avoided for CRISPR by stern vigilance from the start.

4.3. The Patent Problem

One issue that will need to resolved will be the patentability of genetic data. The application of patents to genetic material is especially tricky due to the conflict of intellectual property rights and bioethics, but three main questions can be outlined[14]:

1. How should genetic material be viewed?
    a. A biochemical molecule; or
    b. A scientific tool; or
    c. An element of common heritage; or
    d. With the case of human DNA, information about an individual

2. Do genetic patents provide:
    a. An incentive to encourage the research and application of gene editing; or
    b. A barrier to the access of tools and techniques generated by the research.

3. Which takes precedence?
    a. Private ownership of the fruits of genetic research; or
    b. Public access to the benefits of those products.

There are no easy answers to these questions, as a case can be made for an "all of the above" answer. But aside from the first question, these are issues that need to be discussed about any patent regime[15], and resolving all of them will need amendments to multiple intellectual property laws. Such an endeavour will also be curtailed by international laws such as the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs).

The mere discovery of genes should be not be patentable but gene editing that fulfils the requirement of being sufficiently inventive (the 'inventive step' under the Indian Patent Act, 1970) should enjoy patent protections. This will encourage private R&D into genetic science, which will a crucial role supplementing government funded research in advancing gene editing technologies. However, the exclusive license a patent awards should be reasonably restricted as one of the primary concerns over gene editing lies with the use of gene patents.

Exceptions to the exclusivity already exist under TRIPs such as government use and compulsory licensing but the government should use discretion in employing them, and should make efforts to secure reasonable compensation for the patent holder. An exemption for research purposes should also be maintained in order to foster scientific progress. Intellectual property rights are ultimately intended to serve the interests of the public and not protect the property of an individual. This is why genetic research data on health should also be in the public domain or at the very least be open to the government.

Individuals should also have full IP rights over their genetic data and should be consulted before it is used for any purpose other than what they have consented to. If an individual's genetic data is used to conduct an aggregate study on public health, the data should be anonymised so that positive identification is made difficult.

5. Why is the framework in India's national interest?

Gene Editing can help solve major policy problems in India such as food security and healthcare.

1. **Addressing India's food security issues**

India is the world's largest producer and consumer of pulses, and one of the largest consumers of edible oils. However, pulses are mostly cultivated in poor soils and are dependent on monsoon for water as the majority of arable land in India is dedicated to the production of lucrative crops such as wheat and rice. Domestic pulse production therefore has shockingly low yields - 654 kilograms per hectare, compared with 1,550 kilograms in China and 3,653 kilograms in France, according to data compiled by the Indian Institute of Pulses Research[16]. As such, a considerable amount of India's inflation is driven by fluctuation of pulse prices, while there is also a substantial dependence on imports for them as well as for oilseeds (an estimated 70%).

Furthermore, in the context of global climate change and a rapidly growing population (which is estimated to reach 1.8 billion by 2050), it is all the more vital to turn to whatever means necessary to boost production of foodstuffs. Biotechnological innovations such as gene editing will not only help achieve this but will also lead to better farmer incomes, a healthier population and a reduction in inflation and dependence on imports. A broad consultation by the NITI Aayog in 2015 found that there is a demand among both scientists and farmers for better crop varieties[17]. A substantial leap forward in productivity is required, and cannot be delivered by conventional techniques.

In the international context, it is important to keep in mind that the USA and China have successfully adopted GMOs to a significant extent. 93% of all American cotton, 94% of its soybeans, and 92% of its corn are genetically modified[18]. China, meanwhile, has used commercial GMO crops as a cornerstone of its food security policy since the early 1990s, with tremendous benefits for its farmers, and is positioning itself as a global biotechnology leader[19].

India still relies heavily on imports to feed its population; given the overall trend towards the adoption of GMO crops it would be hypocritical to ban such crops while it continues to import them.

India's food security issues are too dire to instantly reject new technologies like gene editing that could help increase food productivity on principle. A concerted effort should also be made to distinguish the benefits and costs of a technology from the ideal way in which to regulate it. Restraining gene editing because of ineffective regulatory frameworks and opaque testing requirements does not objectively weigh the merits of the technology itself. A failure to rationally consider the adoption of gene editing would not only keep India dependent on foreign food sources and make our agricultural industry less competitive, it would hinder creating a food supply system that could feed millions of hungry Indians.

2. **Improving healthcare technologies**

Genetic disorders such as sickle cell anaemia are widespread in India; it is estimated that 1 out of 10 childhood deaths occurs as a result of genetic disorders[20]. Gene editing research can not only help identifying the underlying gene functions of such diseases for better treatment but provide novel treatments that could help cure and prevent them[21]. In addition, this capacity of gene editing research can also provide a much-needed boost for research on many other diseases such as HIV, muscle dystrophy, cardiomyopathy, and thalassemia.

3. **India already has the resources**

A regulatory environment that mitigates the risks of gene editing but still allows the industry to flourish will enable India to leverage its considerable resources in the field. India is a megadiverse country which harbours 7-8% of all recorded species, including over 45,000 plant species and 91,000 animal species. Meanwhile, 4 out of the 34 biodiversity hotspots in the world are in India: the Western Ghats, the Himalayas, the North-East and the Nicobar Islands[22]. The Convention for Biological Diversity, a binding international agreement signed by India, grants members sovereign rights over genetic resources[23]. As such, India has a vast amount of genetic resources from which gene edited products can be extracted.

These genetic resources are meaningless without the capacity to extract them, which is another area in which India fares well. India is among the 12 destinations for biotechnology in the world and the 3rd ranked country in Asia. It also has a network of over 8.5 million scientists and researchers with established infrastructure in Hyderabad and Bangalore[24]. With both the capacity and the resources India could become a global leader in the field of gene editing.

4. India can become a global leader

The global gene editing market was valued at USD 2.84 billion in 2016 and is projected to reach 5.84 billion by 2021[25]. A majority of this growth is expected to come from the North America, but this is due to the development of gene therapy in the US, the prevalence of gene related diseases (like Alzheimer's and cancer) and a high level of funding.

India also has a prevalence of genetic diseases like sickle cell anaemia and a conducive regulatory framework, along with assistance from the USA and Europe, would significantly boost India's gene editing industry.

Internationally, there is still somewhat of a vacuum on the topic of gene editing[26]. The only legally binding agreement that deals with all aspects of gene editing is the European Union's Oviedo Convention. India is already an independent voice on healthcare in international forums with its stance on generic drugs. A similar stance on gene editing would enable it to earn a strategic advantage in international forums on top of any trade benefits it could earn from having a robust gene therapy industry.

6. How does the Framework address concerns, objections and challenges?

The framework addresses many of the limitations of gene editing. The construction of the Three Level framework addresses many of the concerns about the scientific risks of gene editing by controlling the environment in which it is conducted. The additional requirement of approvals and certification before proceeding with trials or public release also allow ethical concerns about consent and exploitation to be addressed.

6.1 What if the science goes wrong?

As has been mentioned, gene editing technology is not precise. Editing can result in a host of unintended scientific consequences such as off-target effects and mosaicism. The Three Level Framework is designed to specifically prevent these effects from causing meaningful damage. Initial research in laboratories where conditions are controlled contain the damage to a petri dish. The transition from the Laboratory stage to the Trial stage is contingent on the minimisation of these effects to a level of scientific certainty. And it is only once the safety of the application has been exhaustively proved (and verified) that it is cleared for public release at the final stage.

6.2. Won’t gene editing impact the environment?

Environmental impacts are factored in the framework as a serious risk of gene editing technology due to the difficulty of reversing any damage caused. As such, the three stages in the framework address concerns about the environmental impacts. The standards and protocols required to be followed during the first two stages minimise any potential adverse effects a technology may have by controlling the conditions of the experiment in order to contain them.. The additional requirement that ecologists and physicians should be consulted before public release helps ensure that even if the editing safely achieve its purpose, it does not cause knock-on damage to local ecosystems and public health.

6.3. Will the framework prevent the genetic enhancement of humans that would result in 'designer babies' or eugenic programmes?

It has already been pointed out that the level of scientific knowledge required to conduct enhancement of required traits is still very far away and as such, genetic enhancement is still a distant reality[27]. That being said, the Three Level Framework will still be capable of dealing with any research on this topic. Only researchers in Fundamental R&D can conduct research freely on human genetic data, and that too only of certain cells in limited conditions. The need for prior approvals and clearances to proceed in the Commercial R&D and Commercialisation stages respectively can ensure that only gene therapy is allowed and not gene enhancement.

6.4. Will gene editing technologies and products be distributed equally and fairly?

The access to any technology and by extension, the benefits it grants, might be not be distributed equally. This may occur at an international level between developed and developing nations or domestically, where access to the technology is restricted on the basis of grounds like income or profession. This is a valid concern, but the problem stems not from any intrinsic quality of the technology itself, but from its distribution. This can often be attributed to larger systemic issues with financing and property claims.

In India, the major concern is accusations of how the gene editing and seed industries have driven farmers to suicide. But farmer suicides, have been attributed to systemic flaws in agricultural finance rather than simply the sale of gene edited seeds[28][29]. Access should be decoupled from the very concept of gene editing itself; keeping with the spirit of scientific temper, the technology and the ways in which it is used should be viewed separately.

6.5. Gene editing is an unnatural act and should be prohibited

One of the most common refrains against the use of technologies such as CRISPR is based on the notion that it is unnatural to tamper with nature. There are two variants of this argument, the first is accusations of humans playing god. Such arguments, which are primarily based on faith, can often be dogmatic in their formulation, brooking no dissent, no matter how well-reasoned the argument for further scientific progress might be. As such, this document makes no efforts to address that.

The second argument is that gene editing constitutes an undue interference in the gradual process of evolution[30]. This argument is also simplistic in its formulation as it discounts the various ways in which human beings have defied natural processes for centuries of which the domestication of crops and animals are but the first examples. With the advent of IVF treatments and pre-implantation genetic screenings, even human reproduction is not immune to interference. Any drawing of a line now in the context of the usage of new technologies such as CRISPR would be an artificial construct and thus, must be questioned.

7. Conclusion

This paper has extensively discussed the potential, challenges, and risks of gene editing technologies as they stand today. It is clear the many ways in which gene editing can help solve major problems in India like healthcare and food security necessitate allowing India's burgeoning gene industry to thrive. India already has the capacity to become a major player in gene editing and having a thriving local industry would reduce dependence on foreign companies. Indian gene editing companies could not only help improve local conditions but allow India to forge consensus internationally on the use of gene editing in much the same manner as it has done with pharmaceuticals.

The skeleton framework suggested in the paper for India grants the gene editing industry space to thrive but also addresses many of its risks. But as gene editing technology continues to progress a revision would be warranted. The consequences and policy implications of human germline editing, as and when the technology reaches a mature stage, is one such situation. Above and beyond a regulatory framework, a great deal needs to be done to make India more open to scientific progress in general and gene editing in particular. While gene editing is not without its risks and causes for concern, it is undoubtedly capable of being extremely beneficial to the Indian government and humanity at large and it should be given the space to achieve this objective.

Appendices

Appendix A: Benefits of Gene Editing

1. Fundamental Research

A lot of the information currently available on how genes control different aspects of organisms comes from *disrupting* genes and investigating the effects. Although other methods exist for disrupting gene expression, newly discovered methods like CRISPR makes the exercise more accurate and specific. The most immediate and enriching use of gene editing is thus to understand gene functions and to identify which gene sequences play a role in controlling which characteristics in plants, animals, and humans. This fundamental research forms the basis for applied research which could be used for therapeutic or other commercial purposes - not only through gene editing, but also through the development of pharmaceuticals.

2. Plants

Gene editing could be used to address food problems by creating food crops that make agricultural production easier- such as varieties that are drought or pest - resistant or have high- yields. Gene editing can also be used to create crops that make the distribution and marketing of foods easier. For example, the US Department of Agriculture has permitted the sale of a white button mushroom variety genetically edited using CRISPR to resist browning[31]. The application of gene editing need not be restricted to only food crops GMO cotton is already being grown in India.

3. Animals

There are three different ways in which gene editing animals can produce benefits:

a. Food and Animal Husbandry

Animals, for food consumption or domestication uses, can also be gene edited for better yields or ease of use. AquaBounty Technologies made the first FDA- approved gene- edited food, a variety of salmon, for human consumption[32]. These salmon grows to market size in 16 to 18 months instead of the normal 3 three years and have recently begun selling in Canada[33]. Recombinetics, a gene-editing company, has recently created hornless dairy cattle by inserting a gene from hornless beef cattle into milch cattle to make them easier to transport[34]. The hornless cattle are easier to transport. In the US, dairy products have been fermented by CRISPR-edited bacteria edited by CRISPR in the US to be immune to certain viruses and it. It is estimated that almost 50% of US dairy produce in the US is CRISPR-modified[35].

b. Medical Applications

Many gene editing studies are being conducted which, if successful, will have tremendous medical applications. These include editing the genes of animals to remove allergens for producing vaccines, or editing the genes of mosquitoes to preventing mosquitoes them for from carrying malarial parasites, or even animals such as pigs to facilitate organ transplantation from animals such as pigs into human donees.

c. Conservation Efforts.

A third use of gene editing is to preserve species and manage the environment. Research is underway to identify and confer survival genes in bees (to ensure pollination of food crops) and also to help the endangered Indian elephant adapt to cold weather so that it can be released in Siberia. While these applications are currently under-developed, they might be feasible in the future.

4. Humans

The most exciting interesting use of gene editing is in human beings themselves as can be seen from the potential of the following applications:

a. Medical applications

Gene editing can be used to diagnose and treat diseases; research on animal subjects has already begun with this objective. A study from the Salk Institute has shown restoration of sight in animals born with impaired vision[36]. Similarly, scientists have demonstrated the ability to rid animal models of HIV using CRISPR[37]. In 2015, Layla Richards became the first human to receive CRISPR-based treatment for her leukaemia[38].

b. Enhancement of human life

Another potential of gene Gene editing is to can augment humans – by endowing enhanced characteristics such as increased muscle strength, faster metabolism, and so on. Though this use brings up strong ethical considerations, it is important to note the level of current knowledge. While the exact mutations (sequence changes) that cause some diseases have been isolated, there is still scientific uncertainty on how complex traits like muscle strength, skin colour or intelligence are influenced. The technology is, therefore, currently restricted to easier to fixing mutations and genetic diseases like thalassemia;. the The use of gene editing to design babies still requires the unravelling of a lot more knowledge about gene interactions. As such, regardless of ethical concerns, moving ahead without sufficient research is problematic as it and will likely lead to unintended medical consequences such as pleiotropic effects and outcrossing in the near future[39].

Area of Gene Editing Research	*Possible Clinical/Commercial Applications*
In Fundamental R&D	Understanding gene functions and expressions. This is the basis for new or improved therapeutic & commercial applications
Of Plants	Non-transgenic crops, drought-resistant, high-yield, pest-resistant varieties
Of Animals	Higher yields, lower production costs, allergen-free varieties, gene drives, biodiversity, organ transplants with human donees
Of Humans	Treatment of diseases, understanding human biology, enhancement of traits

Table 2.1. ***Possible Applications of Gene-Editing Technologies.***

Appendix B: Scientific Risks

1. Technological Limitations

Older methods of gene editing include meganucleases, zinc finger nucleases, and transcription-activator like effector nucleases (TALENs). These require specialised training, are expensive and have unpredictable side-effects, thus limiting their therapeutic and commercial applications. They differ in the biological components used to execute the edit and in the ease of their implementation in living cells (Table 1). Researchers have previously used meganucleases, ZFNs and TALENs for studying gene functions in the laboratory; some of these studies are also pursuing potential clinical applications for therapeutic purposes.

However, scientists have recently discovered a more precise and relatively cheaper mechanism to perform gene editing - the CRISPR-Cas9 system[40].

The CRISPR-Cas9 system uses a bacterial immune response to cut a specified gene sequence and insert a replacement gene. CRISPR-Cas9's comparative precision has resulted in the method being termed a "molecular scalpel" and has subsequently generated tremendous interest in the scientific community over its potential usage[41]. However, the CRISPR system is a new technology still in its nascent stages and warrants exhaustive research into its side-effects.

In particular, two risks stand out:

a. **Off-target effects** - editing of non-target genes because of sequence similarity with the target gene or genes;

b. **Mosaicism –** uneven editing of cells occurring due to inefficient delivery and non-uniform uptake of the editing machinery by all cells.

These shortcomings of the technology can be used as justifications in suspending further work in the field. However, such an approach goes against one of the fundamental principles outlined at the beginning of this paper, namely, the need to encourage scientific progress. An outright ban would be premature because part of the solution for these problems is through refinement of the technology itself. In fact, with CRISPR, there have been developments that can reduce the scope for error by reducing off-target mutations[42]. What is important, therefore, is the need to provide a framework within which tests and research can be carried out to improve the efficacy of the technology.

Once the efficacy of a particular technology has been suitably demonstrated in controlled environments, a leap of faith will have to be taken in the field of germline modifications. This is similar to the position taken in the UK with respect to mitochondrial replacement therapy (MRT)[43].

Technology	*Ease of Use*	*Precision Editing*	*Existing Clinical/Commercial Applications*
Zinc Finger Nucleases	Construction of some of the biological components requires specialised training and is time consuming.	High precision; however some off-target effects are seen	Clinical trial for the treatment of HIV; Study in mouse[44] models for treatment of Haemophilia B[45] ;Confer herbicide resistance in corn[46] and tobacco[47]
TALENS	Construction of some of the biological components requires specialised training and is time consuming.	High precision; however some off-target effects are seen	Disease-resistant rice[48]; Clinical trial for Leukemia[49]

CRISPR-Cas9	Extremely easy to perform on a variety of cells and cheaper than any other gene-editing technology	High precision; however off-target effects are seen	Clinical trial for treatment of cancer[50]; Mushroom that is resistant to browning[51]

Table 2.2. ***Gene editing technologies and their current usage.***

2. Knowledge Limitations

Even as scientists work on perfecting the technology to edit genes, many are engaged in exploring gene functions. There is a considerable information gap when it comes to how genes control characteristics, which sequences within genes are important, and which sequences need to be altered to effect the required change. There is also a lack of clarity of the side-effects of gene editing in organisms, thus making this application unreliable.

3. Environmental Impact

A major risk of large scale gene editing is the potential impact on the environment. For example, genetic editing of create plants or animals could result in outcrossing - the potential that a gene from an edited organism could transfer into the wild and wreak havoc on natural biodiversity. As such, gene editing could potentially impact not just the wild varieties of the organism edited but the ecosystem which that organism inhabits or neighbours. From a consumption point of view, adverse effects include increased allergenicity.

Gene editing technologies could also impact the environment due to the ways in which they or their resultant products are used rather than any intrinsic quality of the technologies themselves. For example, Monsanto, a major GM multinational, edits plants to be resistant to glysophate, a herbicide that it also sells (branded as Roundup). Reports have emerged that indicate that an over-reliance on Roundup and a drop in the use of other weed reduction methods such as ploughing and tilling may have led to glysophate-resistant weeds dubbed as "superweeds"[52]. Similarly, farmers, chasing the promise of higher yields and profits, may overuse gene edited crops. While gene editing is an immensely powerful tool, it cannot confer resistance to all problems. A gene edited crop that is resistant to drought might still be vulnerable to pests. Thus, if only one gene edited crop is sown in a season ("monoculture"), the entire crop may be lost to due to reasons that the gene editing is unable to combat. Furthermore, if monoculture of one crop is practised repeatedly over seasons ("monocropping") it could impact the fertility of the soil and increase the incidence of pests and weeds.

Gene editing of humans also has environmental risks – outcrossing is just as much a risk with editing human genes as it is with other organisms. There are also other potential large scale implications of human gene editing, as is the case with the treatment of genetic diseases. While they are obviously debilitating, some human genetic diseases do also confer beneficial traits. For example, sickle-cell anaemia may be advantageous to carrier individuals by offering resistance to malaria. If gene editing is used to correct sickle-cell anaemia in all individuals, it could potentially result in increased outbursts of malaria. Those in favour of editing sickle-cell anaemia genes could argue that malaria could be addressed in other ways, such as controlling mosquito populations. But this raises the question of how predators like bats that are dependent on mosquitoes for food would survive and other such broader effects on ecosystems.

As such, any proposal of gene editing must raise and answer questions of the cascading effects that its deployment could result in before it is deployed on a mass scale. This is why most laws and regulations on the environment and gene editing, especially international ones, enforce what is known as the **precautionary principle**. This principle is a reversal of the burden of proof and requires any person seeking to implement a new technology to prove that it is harmless. They cannot merely state that there is no evidence that the technology causes harm. However, given that the intention is to protect the environment, the burden is typically relaxed when the technology has the potential to reverse harm[53].

Appendix C: Ethical Considerations

Discussions on the use of editing of human genes, particularly future generations, have understandably been in the limelight more than any other applications of gene editing. This is law because the technology conflicts with many of the abstract constructs that underpin society such as equality and free will. Bioethics and human rights already and formation it. The ethical considerations of gene editing are various and are discussed below:

1. Individual Autonomy

A belief that individuals, at least on some fundamental level, should be allowed to act according on the basis of their own motives, reasons and desires is an underpinning of most liberal democratic republics. It is the basis of an electoral system of representative democracy and is one of the primary motivations for a human rights framework that protects freedom and equality. It goes without saying that the autonomy of one individual should not enable them to override that of another. Nevertheless, providing agency to people and protecting their freedom to exercise it is a core principle in law that the editing of human genomes could conflict with.

In order to ensure that the editing of human genomes (or any other technology, service or action that has the potential to impact human lives to such an extent) does not impede individual autonomy it must reconcile with the following concepts:

A. Consent

The notion of consent is of particular significance in society as it underpins contractual relationships and criminal offences such as rape. Within the context of scientific research consent is a necessary precursor; any individual subject to gene therapy or research must be made aware of the potential risks involved. Most laws regulating genetic research and its applications have a requirement for free, prior and informed consent from any research participants. The specifics of this requirement can often prove to be problematic in implementation. For example, to what extent can research be conducted when people are unable to provide this consent? The typical examples in medical research are people who are unconscious or have a significant mental disability, but germline editing provides additional difficulties due to its ability to affect subsequent generations.

It can be argued that germline editing results in changes that an unborn child has not consented to. However, it is also the case that parents already *do* have the capacity to choose for their children before they reach majority, i.e. the age of consent.

They even have this ability before they are born, whether it is through conscious selection of partners or through processes such as the genetic screening of embryos.

Even if the ability of parents to choose for their children is assumed, the extent of this ability can be questioned. This is particularly relevant in situations where parents make choices that are arguably not in the best interests of their children[54]. This is a far trickier proposition, and might require the setting of appropriate standards that govern the usage of gene editing. It should be pointed out that standards prescribing a limit on the ability of parents to decide for their children already exist in some jurisdictions, as is the case with child protective services in the USA.

Another concern with consent arises from the sheer pace at which gene editing technologies have progressed. It is quite possible that genetic data collected now could be processed with techniques and processes not imaginable today. The question then is, can that data be legally processed with the new technique when the subject could not have given informed consent about that particular technique. This is one of the primary concerns of the International Declaration on Human Genetic Data, 2003 - an international law dealing solely with genetic data, and not editing or research[55].

B. Confidentiality

A degree of control over sensitive information is a natural extension of personal autonomy. Physician-patient communications are often a protected by confidentiality in a similar manner to attorney-client communications. Aside from the ethical considerations there is also a strong practical argument to protecting confidentiality in medical contexts – patients or subjects are more likely to avail medical services especially with conditions like HIV.

Most medical information can be considered sensitive and personal, but human genetic data is especially so. There is often an expectation on researchers to keep the genetic data of their subjects confidential under the International Declaration on Human Genetic Data as well as with most domestic laws.

2. Eugenics

The use of gene editing can exacerbate inherent inequalities in society through eugenics. This may not even be by design as it is inevitable that at any given point in time, certain traits will be considered by society as being superior. This could lead to a proliferation of these traits by their introduction through gene editing. For instance, one could easily foresee a scenario where fairer skin or male progeny are preferred in an Indian context. More ominously, gene editing could also be used to selectively design a class of 'superior humans'.

Such selective applications of gene editing are only exacerbated by issues of equal access as discussed above. When coupled together, they only increase the likelihood of societal changes being brought about by the elite who have access to the technology.

3. Impact on the rights of the disabled

While gene editing brings with it the promise of treatments for several diseases and disabling medical conditions, questions have been raised about what constitutes a disability itself and the extent of intervention that can be deemed acceptable[56].

This concern must be addressed in the manner in which policies around the use of CRISPR for medical interventions are framed. The easiest solution would be to ensure inclusivity in the process of framing any relevant policies[57].

Appendix D: Classification of Gene-Editing Technology Applications

This table is a summary of the discussion on the position of each application presented in Section 3.

Technology Application	*Target*	*Risk of Unintended Consequences*	*Ethical Considerations*
Gene Editing For Research Purposes Editing for traits intended to be passed down to subsequent generations in small-scale trials	Plants	Low	Low
	Animals	Low	Low
	Humans Cell lines/tissue)	Low	Low
	Humans (Embryos, no implantation)	Low	Low
Lab Trials Growing Organisms to study gene functions	Plants	Low	Low
	Animals	Low	Medium
Field Trials Scaled-up version of lab trials in an open environment	Plants	Medium	Low
	Animals	Medium	Medium
Pre-Clinical Trials The testing of intended human interventions on animals (such as rats, dogs, pigs or primates) for assessment of safety before proceeding with clinical trials.	Animals	Low	Medium
Clinical Trials Trials for testing the safety and efficacy of intended interventions.	Humans (Somatic)	Medium	Medium
	Humans (Germline)	High	Medium

Sale Products being available on the open market	Edited Crops	High	High
	Edited Animals	High	High
Treatment Gene editing technologies aimed at treating pre-existing medical conditions in humans.	Humans	High	Very High
Enhancement Gene editing technologies aimed at selecting and/or increasing human attributes such as intelligence and muscle strength.	Humans	Very High	Extremely High

Appendix E: Intellectual Property Considerations

Intellectual property regimes, especially patents, have historically been constructed to further national interests, namely domestic production, and have traditionally tended to balance societal and private interests[58]. The most common justification for a patent system is to encourage innovators to undergo often expensive research by promising financial rewards at the end of their labours. This however, requires granting a temporary monopoly on the technology to the inventor that may restrict the dissemination of a technology that may be beneficial to society. The trade-off is considered worthwhile if the net result is fast-tracked scientific progress, but the empirical basis of this cause-effect assumption is questionable[59].

Complex and strong patent regimes generally require a developed manufacturing and agricultural infrastructure, and tend to be created as a consequence of development rather than act as a precursor to progress[60].

It should be clarified that patents are only valid in a particular jurisdiction. Though international organisations such as the World Intellectual Property Organisation (WIPO) allow inventors to apply for patents in multiple countries, patents are only granted at the national level and patent legislation is designed and applied at a national level. However, states are severely curtailed in their ability to consider national interests when designing domestic patent laws by international agreements such as the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which is between members of the World Trade Organisation (WTO).

The WTO and TRIPS are both dominated by the US government, which is in turn heavily influenced by multinational companies with extensive IP portfolios. The end result is a protectionist IPR regime that protects their interests more than those of developing nations and also consider seeds licensed commodities instead of the traditional view of seeds being a part of common human heritage[61]. New legal standards were created in determining patents such as whether the gene was a "natural product" or contained "human intervention"[62].

Patents for genetic technology were also allowed to be filed as utility patents, rather than plant or gene patents, allowing patent holders to restrict the sale and reuse of any product that originated from any technology which provided a novel use or "utility" (which in the case of genetics would cover any modification or added trait).

Given the complexities of viewing patents on genetic research outlined above, a debate must be conducted on the worth of granting an exclusive license to genetic research, and the extent to which it should be exclusive. This debate should also examine the international dimensions of genetic research in terms of sovereign rights over genetic material and the relationship between developed and developing countries. Exceptions to the exclusive license of patents already exist. A few of these are discussed in brief below:

1. Compulsory Licensing

Compulsory licence is a licence granted by an administrative or a judicial body to a third party without the consent of the patent holder. There are two primary components of compulsory licensing. The first is that there should be some compelling reason to violate the exclusive license of the patent holder which include public interest, anti-competition, emergencies or a refusal of the holder to exploit the patent. The second is that it should generally be at the end of an administrative or judicial process where efforts are made to co-operate with the patent holder such as the offer of compensation.

2. Public, Non-Commercial Use (Government Use)[63]

The concept of patents has been described as a Faustian bargain, in that inventors reveal the full workings of their invention to the government, which then promises them a temporary exclusive license over the invention. As such, under common law, the government is considered to have eminent domain over the patent and the use of this patent is not considered a patent violation.

Government use and compulsory licensing have many similarities but differ in key ways. There is no requirement for governments to attempt to secure a voluntary license and the procedural requirements are generally less onerous than compulsory licenses. The primary difference is that government use is only for 'public and non-commercial use' while compulsory licences cover private and commercial use.

3. Research exemptions

Many states also allow research to be conducted on patented technologies provided that it does not unreasonably conflict with the normal exploitation of the patent or prejudice the rights of the patent holder.

REFERENCES

[1] Berg, Paul. "Meetings that changed the world: Asilomar 1975: DNA modification secured". Nature. Last accessed 10 October 2017
http://www.nature.com/nature/journal/v455/n7211/full/455290a.html?foxtrotcallback=true
[2] A full description of the benefits of gene editing can be found in Appendix A
[3] "CRISPR Gene Editing can Cause Hundreds of Unintended Consequences". *Columbia University Medical Center*. Last accessed on 10 October, 2017.
http://newsroom.cumc.columbia.edu/blog/2017/05/30/crispr-gene-editing-can-cause-hundreds-of-unintended-mutations/
[4] Le Page, Michael. "Mosaic problem stands in the way of gene editing embryos". *New Scientist.* Last accessed on 10 October, 2017. https://www.newscientist.com/article/mg23331174-400-mosaic-problem-stands-in-the-way-of-gene-editing-embryos/
[5] A more detailed description of the scientific risks and ethical considerations of gene editing can be found in Appendices B and C respectively.
[6] Tusk, Bradley. "Shockingly, Congress acted responsibly in regulating autonomous cars… So what's next?" Last accessed 10 October, 2017. https://techcrunch.com/2017/09/10/shockingly-congress-acted-responsibly-in-regulating-autonomous-cars-so-whats-next/
[7] Blogs, Menu SLS |SLS, and Hank Greely. "Of Science, CRISPR-Cas9, and Asilomar." Stanford Law School. Last accessed 11 July 2017. https://law.stanford.edu/2015/04/04/of-science-crispr-cas9-and-asilomar/
[8] Supra Note 1
[9] "Genome Editing: An Ethical Review" *The Nuffield Council on Bioethics*, September. 2016. Web. pp. 24.
[10] "Nothing to Sneeze At: The Allergenicity of GMOs." Science in the News. August 14, 2015. http://sitn.hms.harvard.edu/flash/2015/allergies-and-gmos/
[11] NBC.com. "'Superweeds' Sprout Farmland Controversy Over GMOs." NBCNews.com. September 30, 2014. https://www.nbcnews.com/business/economy/superweeds-sprout-farmland-controversy-over-gmos-n214996
[12] One possible criteria for evaluating open field trials for crops can be substantial equivalence - the researchers must demonstrate must demonstrate that it is not substantially altered from the non-GM crop in terms of its use as food or feed, or in terms of its environmental safety.
[13] While this may lead to a risk of "technology censorship" that restricts a free market, it is a necessary trade off as even a minor market failure can lead to disastrous and potentially irreversible consequences.
[14] "Genetics, Genomics and the Patenting of DNA: Review of potential implications for health in developing countries" World Health Organisation. Last accessed July 17, 2017 at http://www.who.int/genomics/publications/executivesummary/en/
[15] See Appendix E.
[16] Rastello, Sandrine. "An Upgraded 3,000-Year-Old Pea Could Ease India's Inflation Problem." *Bloomberg.com*. July 19, 2016. Last accessed 11 July 2017.
https://www.bloomberg.com/news/articles/2016-07-19/an-upgraded-3-000-year-old-pea-could-ease-india-s-inflation-problem
[17] Raising Agricultural Productivity and Making Farming Remunerative for Farmers". Published by *NITI Aayog*, 16 December 2015. Last accessed 12 July 2017.
[18] "Recent Trends in GE Adoption." *USDA ERS - Recent Trends in GE Adoption*. Last accessed 11 July 2017. https://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-us/recent-trends-in-ge-adoption.aspx.
[19] Huang et al, 2005.

[20] Rao VB, Ghosh K. Chromosomal variants and genetic diseases, *Int. J. Hum. Gen.*, 2005, vol. 11 (pg. 59-60)
[21] Ibid
[22] India's Fifth National Report to the Convention on Biological Diversity 2014
https://www.cbd.int/doc/world/in/in-nr-05-en.pdf
[23] Article 15(1) of the Convention on Biological Diversity
[24]Frost & Sullivan: India Ripe for Biotech Industry Growth. Last accessed 10 October 2017
http://images.discover.frost.com/Web/FrostSullivan/FS_WP_CII%20India%20Biotech%20Road%20Map_052516_CAM-v2.pdf.
[25] http://www.marketsandmarkets.com/PressReleases/genome-editing-engineering.asp
[26] "India should take the lead on the gene editing debate". Hindustan Times. Last accessed on 10 October, 2017 http://www.hindustantimes.com/editorials/india-should-take-the-lead-on-the-gene-editing-debate/story-Cfyrp3kAik2evqLhI7mVOM.html
[27] Blogs, Menu SLS |SLS, and Hank Greely. "Of Science, CRISPR-Cas9, and Asilomar." Stanford Law School. Last accessed 11 July 2017. https://law.stanford.edu/2015/04/04/of-science-crispr-cas9-and-asilomar/
[28] Gruere, Guillaume., Mehta-Bhatt, Purvi., and Debdatta Sengupta. "BT Cotton and Farmer Suicides In India. "International Food Policy Research Institute. October 2008. Last accessed 12th July 2017. http://cdm15738.contentdm.oclc.org/utils/getfile/collection/p15738coll2/id/14501/filename/14502.pdf
[29] Andrew Paul Gutierrez, Luigi Ponti, Hans. R. Herren, Johann Baumgärtner, and Peter Kenmore. "Deconstructing Indian Cotton: Weather, Yields, and Suicides." Environmental Sciences Europe 27, no. 1. June 2015. Last accessed 12 July 2017. doi:10.1186/s12302-015-0043-8.https://enveurope.springeropen.com/track/pdf/10.1186/s12302-015-0043-8?site=enveurope.springeropen.com
[30] Jim Kozubek. "How CRISPR and Gene Editing Could Ruin Human Evolution." Time. Last accessed 11 July 2017. http://time.com/4626571/crispr-gene-modification-evolution/
[31] Waltz, Emily. "Gene-edited CRISPR Mushroom Escapes US Regulation." Nature News. Last accessed 04 July 2017. http://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754.
[32] Ledford, Heidi. "Salmon is first transgenic animal to win US approval for Food". Nature. November 19, 2015. Last accessed September 21, 2017
https://www.nature.com/news/salmon-is-first-transgenic-animal-to-win-us-approval-for-food-1.18838/
[33] Waltz, Emily. "First genetically engineered salmon sold in Canada". Nature. August 04, 2017. Last accessed September 21, 2017
https://www.nature.com/news/first-genetically-engineered-salmon-sold-in-canada-1.22116
[34] Loria, Kevin. "Cows with Horns May Soon Be a Relic of Farming's Painful past." Business Insider. May 12, 2016. Last accessed July 11, 2017. http://www.businessinsider.com/recombinetics-genetically-edited-cattle-without-horns-2016-5?IR=T
[35] Peters, Adele. "CRISPR Is Going To Revolutionize Our Food System-And Start A New War Over GMOs." Fast Company. April 13, 2016. Last accessed July 04, 2017.
https://www.fastcompany.com/3056693/crispr-is-going-to-revolutionize-our-food-system-and-start-a-new-war-over-gmos
[36] Keilchiro Suzuki et al. "In Vivo Genome Editing via CRISPR/Cas9 mediated homology-independent targeted integration." Nature News. December 1, 2016. Last accessed 12 July 2017.
https://www.nature.com/nature/journal/v540/n7631/full/nature20565.html
[37] Yin Chaoran."In Vivo Excision of HIV-1 Provirus by Cas9 and Multiplex Single-Guide RNAs in Animal Models" Molecular Therapy. Volume 25. May 3, 2017, Last accessed 12 July 2017.
http://www.sciencedirect.com/science/article/pii/S1525001617301107
[38] Le Page, Michael."Gene Editing Saves Girl Dying from Leukaemia in World First." New Scientist. Last accessed 11 July 2017. https://www.newscientist.com/article/dn28454-gene-editing-saves-life-of-girl-dying-from-leukaemia-in-world-first/

[39] Pleiotropic effects are simultaneous manifestations of different effects caused by the same change - for example, if a gene for protein transport in cells is edited, all proteins that are carried by that transporter will be affected resulting in multiple different effects.
[40] Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J.A., and Charpentier, E. (2012). A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 337, 816–821
[41] Pennissi, Elizabeth. "Popular Gene-editing Technique Gets Sharper Molecular Scissors." Science | AAAS. February 03, 2016. Last accessed 12 July 2017. https://www.sciencemag.org/news/2015/09/popular-gene-editing-technique-gets-sharper-molecular-scissors.
[42] Zhang, Sarah. "Crispr Is Getting Better. Now It's Time to Ask the Hard Ethical Questions." Wired. December 01, 2015. Last accessed 11 July 2017. https://www.wired.com/2015/12/stop-dancing-around-real-ethical-problem-crispr/
[43] "Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review." The Nuffield Council of Bioethics. Last accessed June, 2012. Web. pp. 88.
[44] Tebas et al. "Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV." New England Journal for Medicine. April 6, 2014. Last accessed 13 July 2017. 370:901-910
[45] Sharma et al, "In vivo genome editing of the albumin locus as a platform for protein replacement therapy." Blood. August 2015. Last accessed 13 July 2017
[46] Shukla et al, "Precise genome modification in the crop species Zea mays using zinc-finger nucleases". Nature News. April 29, 2009. Last accessed 13 July 2017
[47] Townsend et al, "High-frequency modification of plant genes using engineered zinc-finger nucleases." Nature News. May 21, 2009. Last accessed 13 July 2017
[48] Li et al, "High-efficiency TALEN-based gene editing produces disease-resistant rice"2012. Last accessed 13July 2017.
[49] Qasim et al, "Molecular Remission of Infant B-All After Infusion of Universal TALEN Gene-Edited CAR T Cells."2017. Last accessed 13 July 2017
[50] Reardon, Sara. "First CRISPR Clinical Trial Gets Green Light from US Panel." Nature News. Last accessed 04 July 2017. http://www.nature.com/news/first-crispr-clinical-trial-gets-green-light-from-us-panel-1.20137.
[51] Waltz, Emily. "Gene-edited CRISPR Mushroom Escapes US Regulation." Nature News. Last accessed 11 July 2017. http://www.nature.com/news/gene-edited-crispr-mushroom-escapes-us-regulation-1.19754
[52] CNBC.com. "'Superweeds' Sprout Farmland Controversy Over GMOs." NBCNews.com. September 30, 2014. Accessed August 07, 2017. http://www.nbcnews.com/business/economy/superweeds-sprout-farmland-controversy-over-gmos-n214996.
[53] Principle 15 of the United Nations Conference on Environment and Development". http://www.un.org/documents/ga/conf151/aconf15126-1annex1.htm.
[54] Editing Humanity, supra note 2. The article raises the possibility of hearing-impaired parents seeking to edit embryos to produce deaf offspring. This particular scenario involves more than the idea of consent, however. It is also connected to the discourse around disability rights, discussed subsequently.
[55] International Declaration on Human Genetic Data | United Nations Educational, Scientific and Cultural Organization. http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genetic-data/
[56] Erica Check Hayden. "Should You Edit Your Children's Genes?" Nature News. Last accessed 11 July 2017. http://www.nature.com/news/should-you-edit-your-children-s-genes-1.19432
[57] The movement is best exemplified by the saying, 'Nothing About Us, Without Us', a rallying cry that seeks equal representation in discussions around disability rights.
[58] Stein, Haley. "Intellectual Property and Genetically Modified Seeds: The United States, Trade, and the Developing World" in Northwestern Journal of Technology and Intellectual Property. Volume 3,

Issue 2, Spring 2005. Last accessed July 17, 2017 at
http://scholarlycommons.law.northwestern.edu/cgi/viewcontent.cgi?article=1033&context=njtip

[59] Archibugi, Daniele and Filippetti, Andrea. "The Globalisation of Intellectual Property Rights: Four Learned Lessons and Theses" in Global Policy Voume 1, Issue 2. Accessed July 17, 2017 at http://www.danielearchibugi.org/downloads/papers/IPRglobalization.pdf

[60] Supra Note 57

[61] Ibid

[62] Ibid

[63] Supra Note 50